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Nutritional status, mitochondrial function and aerobic capacity as biomarkers of illness course in acute episodes of bipolar disorder

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NUTRITIONAL STATUS, MITOCHONDRIAL FUNCTION AND AEROBIC CAPACITY AS BIOMARKERS OF ILLNESS COURSE IN ACUTE EPISODES OF BIPOLAR DISORDER

Doctoral thesis dissertation presented by Anna Giménez Palomo to apply for the degree of doctor at the University of Barcelona

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Acronyms and abbreviations

ADHD: attention deficit/hyperactivity disorder

ADP: adenosine diphosphate

α-LA: alpha-lipoic acid

AMP: adenosine mohophosphate

AMPK: AMP-activated protein kinase

APA: American Psychiatric Association

ASPEN: American Society for Parenteral and Enteral Nutrition

ATP: adenosine triphosphate

AUC: area under de ROC curve

AUDIT: Alcohol Use Disorders Identification Test

BD: bipolar disorder

BDNF: brain-derived neurotrophic factor

BMI: body mass index

CaMKK2: Calcium/Calmodulin Dependent Protein Kinase Kinase 2

CAT: catalase

CCCP: 3-chlorophenylhydrazone

ccf-mtDNA: circulating cell free mitochondrial DNA

CGI-I: Clinical Global Impression Scale – Improvement

CGI-S: Clinical Global Impression Scale – Severity

CK: creatine kinase

CONUT: Controlling Nutritional Status

COPD: chronic obstructive pulmonary disease

CoQ_{10}: coenzyme Q_{10}

CPET: cardiopulmonary exercise test

CREB: cAMP-response element binding protein

CWRCE: constant work rate cycle ergometry

DAMPs: damage-associated molecular patterns

DAT: dopamine transporter

DSM: Diagnostic and Statistical Manual of Mental Disorders

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

ECT: electroconvulsive therapy

ESPEN: European Society for Clinical Nutrition and Metabolism

ETC: electron transport chain

FAST: Functioning Assessment Short Test

FEV_1: forced expiratory volume in the first second

FFMI: fat-free mass index

GLIM: Global Leadership Initiative on Malnutrition

GNRI: Geriatric Nutritional Risk Index

GPx: glutathione peroxidase

GR: glutathione reductase

GSH: glutathione

GSK-3: glycogen synthase kinase-3

GWAS: genome-wide association studies

HC: healthy controls

HDRS: Hamilton Depression Rating Scale

ICD-11: International Classification of Diseases, 11th Edition

IDF: International Diabetes Federation

IL-1β: interleukin-1β

IL-6: interleukin-6

IPAQ: International Physical Activity Questionnaire

iPSC: induced pluripotent stem cells

IQR: interquartile range

MAC: midarm circumference

MAMs: mitochondria-associated membranes

MetS: metabolic syndrome

MIM: mitochondrial inner membrane

MNA: Mini Nutritional Assessment

MNA-SF: Mini Nutritional Assessment Short Form

mtDNA: mitochondrial DNA

MOM: mitochondrial outer membrane

mPTP: mitochondrial permeability transition pore

MUST: Malnutrition Universal Screening Test

NAA: N-acetyl-aspartate

NAC: *N*-acetylcysteine

nDNA: nuclear DNA

NFκβ: nuclear factor kappa beta

NLRP3: nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3

NRI: Nutritional Risk Index

NRS-2002: Nutritional Risk Screening 2002

OABD: Older Adults with Bipolar Disorder

OCR: oxygen consumption rate

OR: odds ratio

OXPHOS: oxidative phosphorylation

PBMC: peripheral blood mononuclear cell

PCr: phosphocreatine

PKA: protein kinase A

PKC: protein kinase C

PNI: Prognostic Nutritional Index

PREDIMED-17: 17-point questionnaire to assess adherence to the energy-restricted Mediterranean diet

RF: random forest

ROS: reactive oxygen species

SD: standard deviation

SGA: Subjective Global Assessment

SIRT: sirtuin

SOD: superoxide dismutase

TCA: tricarboxylic acid

TLR9: toll-like receptor 9

TNF: tumor necrosis factor

TSF: triceps skinfold thickness

VIF: variation inflation factor

VO_2peak: maximum oxygen uptake

YMRS: Young Mania Rating Scale

List of articles comprised in the thesis

The present doctoral thesis has been conducted in the format of a compendium of articles and comprises one primary objective and ten secondary objectives. To achieve this, four original articles have been included.

1. Giménez-Palomo, A., Gomes-da-Costa, S., Borràs, R., Pons-Cabrera, M. T., Doncel-Moriano, A., Arbelo, N., Leyes, P., Forga, M., Mateu-Salat, M., Pereira-Fernades, P. M., Benabarre, A., Pacciarotti, I., Vieta, E. (2023). Effects of malnutrition on length of stay in patients hospitalized in an acute psychiatric ward. *Acta Psychiatrica Scandinavica, 148(4),* 316-326. Doi: 10.1111/acps.13598. IF; Quartile (JCR 2022): 6.7; Q1.
2. Giménez-Palomo, A., Guitart-Mampel, M., Meseguer, A., Borràs, R., García-García, F. J., Tobías, E., Valls, L., Alsina-Restoy, X., Roqué, G., Sánchez, E., Roca, J., Anmella, G., Valentí, M., Bracco, L., Andreu, H., Salmerón, S., Colomer, L., Radua, J., Verdolini, N., Berk, M., Vieta, E., Garrabou, G., Pacchiarotti, I. (2024). Reduced mitochondrial respiratory capacity in patients with acute episodes of bipolar disorder: Could bipolar disorder be a state-dependent mitochondrial disease?. *Acta Psychiatrica Scandinavica, 149(1)*, 52-64. Doi: 10.1111/acps.13635. IF; Quartile (JCR 2022): 6.7; Q1.
3. Giménez-Palomo, A., Guitart-Mampel, M., Roqué, G., Sánchez, E., Borràs, R., Meseguer, A., García-García, F. J., Tobías, E., Valls-Roca, L., Anmella, G., Valentí, M., Olivier, L., de Juan, O., Ochandiano, I., Andreu, H., Radua, J., Verdolini, N., Berk, M., Vieta, E., Garrabou, G., Roca, J., Alsina-Restoy, X., Pacchiarotti, I. (2022). Aerobic capacity and mitochondrial function in bipolar disorder: a longitudinal study during acute phases and after clinical remission. *Frontiers in Psychiatry, 26:15:*1386286. Doi: 10.3389/fpsyt.2024.1386286. IF; Quartile (JCR 2022): 4.7; Q2.
4. Giménez-Palomo, A., Fico, G., Andreu, H., Olivier, L., Salmerón, S., Ochandiano, I., de Juan, O., Fernández-Plaza, T., Colomer, A., Mateu-Salat, M., Borràs, R., Vieta, E., Pacchiarotti, I. Analyzing Nutritional and Metabolic Factors for Predicting Malnutrition and Readmission Following a Manic Episode in Bipolar Disorder: A Machine Learning Approach. Submitted. Non-published data.

Total Research Line IF: 18.1

Resum

Títol: Estat nutricional, funció mitocondrial i capacitat aeròbica com a biomarcadors de curs de malaltia en episodis aguts del trastorn bipolar.

Introducció:

El trastorn bipolar (TB) és un trastorn psiquiàtric amb una prevalença del voltant del 2,4%, caracteritzat per episodis recurrents de depressió, mania o hipomania, alternats amb períodes d'eutímia, el qual suggereix un patró bifàsic de disponibilitat d'energia en aquesta malaltia. Tot i un tractament adequat, el TB està associat amb una reducció en la qualitat de vida i en el funcionament psicosocial, especialment en aquells pacients amb un major nombre de recaigudes. Els pacients amb TB presenten una major prevalença de comorbiditats psiquiàtriques però també mèdiques, especialment metabòliques, i d'un estat nutricional deficient, en comparació amb la població general. No obstant, l'impacte de l'estat nutricional en el curs de la malaltia ha estat escassament descrit.

Hipòtesis:

En el TB, s'observarà un patró bifàsic de disponibilitat energètica, amb un increment en mania i una reducció en depressió, en comparació amb l'eutímia, el qual s'observarà tant mitjançant anàlisis de respiració mitocondrial com de capacitat aeròbica durant l'exercici físic. També s'observaran diferències en la capacitat de respiració mitocondrial entre episodis aguts de TB i controls sans. Així doncs, es trobarà una correlació positiva entre capacitat aeròbica i respiració mitocondrial tant durant descompensacions afectives com en eutímia. Tanmateix, pacients ingressats en una unitat d'hospitalització de Psiquiatria, especialment aquells amb TB, presentaran alteracions nutricionals i metabòliques associades amb el curs de la malaltia a curt termini, influint sobre la durada de l'hospitalització, i a llarg termini, associant-se amb el nombre de recaigudes en els anys següents.

Objectius:

L'objectiu principal consisteix a identificar si existeixen variacions en paràmetres bioenergètics entre episodis aguts del TB i la remissió simptomàtica, mitjançant l'estudi de la capacitat de consum d'oxigen de la cadena de transport d'electrons (CTE)

mitocondrial i la capacitat aeròbica durant l'exercici físic. A més, aquest projecte té els objectius de comparar diferències en la capacitat de consum d'oxigen de la CTE mitocondrial entre episodis de descompensació afectiva en pacients amb TB i controls sans, determinar la correlació entre la capacitat de respiració mitocondrial i la capacitat aeròbica en diferents fases de la malaltia, per a la identificació de potencials biomarcadors dependents de la fase del TB. Entre els objectius secundaris també s'inclou la caracterització del perfil nutricional en pacients ingressats en una unitat d'hospitalització de Psiquiatria, especialment en pacients amb TB, i determinar si aquest s'associa amb marcadors de curs de malaltia a curt o llarg termini, incloent la durada de l'hospitalització i els reingressos per descompensació afectiva en els propers tres anys.

Mètodes:

Es van dur a terme 4 estudis clínics, un d'ells transversal i tres de caire longitudinal. Tots d'ells van incloure pacients ingressats en la sala d'aguts de Psiquiatria de l'Hospital Clínic de Barcelona.

- **Estudi I**: es van caracteritzar el perfil nutricional de pacients ingressats i es va analitzar l'associació entre factors nutricionals i durada de l'hospitalització.
- **Estudi II**: es van incloure pacients amb TB hospitalitzats per un episodi agut de la malaltia, es va realitzar una avaluació clínica i es va analitzar la capacitat de respiració mitocondrial en cèl·lules polimorfonuclears obtingudes a partir d'una extracció sanguínia, tant en l'episodi agut com en remissió clínica.
- **Estudi III**: es va incloure un subgrup de pacients compresos en l'estudi II, en els quals es van realitzar, a banda de les avaluacions clíniques i anàlisis de respiració mitocondrial, proves d'esforç en un cicloergòmetre per a l'estudi de la capacitat aeròbica, també en l'episodi agut i en remissió clínica. Aquestes proves es van dur a terme al Centre de Diagnòstic Respiratori de l'Hospital Clínic de Barcelona.
- **Estudi IV**: es va analitzar, a partir d'una mostra de pacients ingressats per un episodi maníac entre els anys 2015 i 2019, l'associació entre diferents factors nutricionals i metabòlics i el nombre de reingressos per episodis afectius en els següents tres anys, així com la capacitat dels factors estudiats per predir el risc de desnutrició i de reingressos, segons un model d'aprenentatge automàtic.

Resultats principals:

- **Estudi I:** els nivells de proteïnes plasmàtiques, ferro i la saturació de transferrina van estar inversament correlacionats amb la durada de l'hospitalització. L'estat nutricional es va veure reflectit pels nivells de colesterol, albúmina, zinc, ferro, prealbúmina, transferrina, triglicèrids, saturació de transferrina, recompte de limfòcits i índex de massa corporal (IMC).
- **Estudi II:** la capacitat de consum d'oxigen mitocondrial va ser menor en pacients amb TB durant un episodi maníac o depressiu en comparació amb la remissió clínica. La depressió bipolar es va associar amb menors nivells de capacitat respiratòria mitocondrial en comparació amb la mania.
- **Estudi III:** entre els episodis afectius aguts i la remissió clínica, no es van objectivar diferències significatives en la capacitat aeròbica durant una prova d'esforç . En remissió clínica, el consum d'oxigen previ a l'exercici va mostrar una tendència cap a una correlació negativa amb la capacitat màxima de consum d'oxigen mitocondrial, i el consum màxim d'oxigen durant l'exercici es va correlacionar de manera inversa amb la respiració mitocondrial basal.
- **Estudi IV:** la determinació del risc de desnutrició segons la puntuació *Controlling Nutritional Status* (CONUT) no va predir el curs de la malaltia en el TB. No obstant, paràmetres específics, com nivells menors de glucosa basal, un increment del recompte de leucòcits, un major IMC i nivells més elevats de colesterol total durant un episodi maníac es van associar amb una major probabilitat de reingrés psiquiàtric als tres anys.

Conclusions:

Determinats paràmetres bioenergètics i nutricionals es troben associats amb el curs de la malaltia en individus amb TB. Específicament, la capacitat de consum d'oxigen cel·lular podria actuar com un marcador d'estat de la malaltia, donat que en els episodis aguts del TB es troba reduïda en comparació amb la remissió clínica, mentre que certs paràmetres analítics mesurats en els episodis aguts podrien predir un curs més tòrpid de la malaltia. Aquestes troballes han de ser confirmades en futurs estudis per tal d'identificar biomarcadors que permetin un maneig individualitzat dels pacients amb TB, i determinar perfils amb un major risc de presentar un curs desfavorable de la malaltia, el qual afavoriria el disseny d'estratègies preventives i una milloria en la qualitat de vida en individus amb TB.

Abstract

Title: Nutritional status, mitochondrial function and aerobic capacity as biomarkers of illness course in acute episodes of bipolar disorder.

Introduction:

Bipolar disorder (BD) is a psychiatric disorder with a prevalence of around 2.4%, characterized by recurrent episodes of depression, mania, or hypomania, alternating with periods of euthymia, which suggests a biphasic pattern of energy availability in this disease. Despite adequate treatment, BD is associated with reduced quality of life and psychosocial functioning, especially in those patients with a higher number of relapses. Patients with BD present a higher prevalence of psychiatric but also medical comorbidities, especially metabolic, and a deficient nutritional status, compared to the general population. However, the impact of nutritional status on the course of the disease has been scarcely described.

Hypotheses:

In BD, a biphasic pattern of energy availability will be observed, with an increase in mania and a decrease in depression, compared to euthymia, which will be observed through analyses of mitochondrial respiration and aerobic capacity during physical exercise. Differences in mitochondrial respiration capacity will also be observed between acute episodes of BD and healthy controls. Thus, a positive correlation between aerobic capacity and mitochondrial respiration will be found both during affective episodes and in euthymia. Moreover, patients admitted to a Psychiatry hospitalization unit, especially those with BD, will present nutritional and metabolic alterations associated with the course of the disease in the short term, influencing the duration of hospitalization, and in the long term, associating with the number of relapses in subsequent years.

Objectives:

The main objective is to identify potential variations in bioenergetic parameters between acute episodes of BD and symptomatic remission, by studying the oxygen consumption capacity of the mitochondrial electron transport chain (ETC) and aerobic capacity during physical exercise. Additionally, this project aims to compare differences in the oxygen consumption capacity of the mitochondrial ETC between acute mood episodes in patients with BD and healthy controls, and determine the correlation between

mitochondrial respiration capacity and aerobic capacity in different phases of the disease, for the identification of potential state-dependent biomarkers in BD. Secondary objectives include characterizing the nutritional profile of patients admitted to a Psychiatry hospitalization unit, with a special focus on BD, and determining its association with markers of illness course in the short or long term, including the duration of hospitalization and readmissions for acute mood episodes in the following three years.

Methods:

Four clinical studies (one cross-sectional study and three longitudinal studies) were conducted. All of them included patients admitted to the acute psychiatric ward of Hospital Clínic of Barcelona.

- **Study I**: the nutritional profile of patients admitted was characterized, and the association between nutritional factors and length of stay was studied.
- **Study II**: admitted BD patients were included during an acute mood episode. A clinical assessment was performed, followed by the study of mitochondrial respiratory capacity in polymorphonuclear cells obtained from a blood sample.
- **Study III**: a subsample from the Study II was included. Apart from clinical evaluations and mitochondrial respiration analyses, patients underwent exercise effort tests on a cycle ergometer to study aerobic capacity during both acute episodes and clinical remission. These tests were conducted at the Respiratory Diagnostic Center of the Hospital Clínic of Barcelona.
- **Study IV**: this study included a sample of patients admitted due to a manic episode between 2015 and 2019, and examined the association between nutritional and metabolic factors and the number of readmissions due to affective episodes over the following three years. This study also assessed the ability of the studied factors to predict the risk of malnutrition and readmissions using a machine learning algorithm.

Main results:

- **Study I:** plasmatic protein levels, iron, and transferrin saturation were inversely correlated with the length of stay. Nutritional status was reflected by levels of cholesterol, albumin, zinc, iron, prealbumin, transferrin, triglycerides, transferrin saturation, lymphocyte count, and body mass index (BMI).
- **Study II:** mitochondrial oxygen consumption capacity was lower in patients with BD during a manic or depressive episode compared to clinical remission. Bipolar

depression was associated with lower levels of mitochondrial respiratory capacity compared to mania.

- **Study III:** no significant differences in aerobic capacity were observed during an effort test between acute affective episodes and clinical remission. In euthymia, pre-exercise oxygen uptake tended to negatively correlate with maximal mitochondrial oxygen consumption capacity, and maximal oxygen uptake during exercise inversely correlated with basal mitochondrial respiration.
- **Study IV:** The determination of malnutrition risk according to the Controlling Nutritional Status (CONUT) score did not predict the course of the disease in BD. However, specific parameters, such as lower fasting glucose levels, increased leukocyte count, higher BMI, and higher total cholesterol levels during a manic episode were associated with a greater likelihood of psychiatric readmission within three years.

Conclusions:

Determined bioenergetic and nutritional parameters are associated with the course of illness in individuals with BD. Specifically, cellular oxygen consumption capacity could act as a state marker of the disease, given that it is reduced in acute episodes of BD compared to clinical remission, while certain analytical parameters measured in acute episodes could predict a more torpid course of the disease. These findings need to be confirmed in future studies in order to identify biomarkers that allow individualized management of patients with BD and to determine profiles with a higher risk of presenting an unfavorable course of the illness, which would enable the design of preventive strategies and an improvement in quality of life in individuals with BD.

1. INTRODUCTION

1.1. Bipolar disorder

1.1.1. Definition and epidemiology

Bipolar disorder (BD) is a chronic mental illness characterized by the presence of depressive, manic or hypomanic episodes, which can appear with mixed features in some occasions, alternated with periods of clinical remission or euthymia (1,2). Even being properly treated, in the long term, this disease often impacts negatively patients' quality of life and psychosocial functioning, especially in those individuals with depressive symptoms, a higher number of previous episodes, longer illness duration and lower cognition (3).

Several psychiatric comorbidities are common in individuals with BD, such as anxiety disorders, attention-deficit/hyperactivity disorder, personality disorders, and substance use disorders (4). Patients with BD also display an increased prevalence of medical comorbidities compared to general population (5).

BD has an estimated prevalence of 2.4%, including BD types I (BD I) and II (BD II) (3). BD typically manifests during late adolescence or young adulthood, with an average age of onset of 25 years (3). A delay to diagnosis and treatment of BD is often found in patients with early age of onset. Whereas BD II is more prevalent in females, BD I has a similar prevalence between males and females (6). Despite both genetic and environmental factors have been associated with BD, BD has a considerably high heritability rate compared to other mental disorders, which is around 60% (7,8). It is a polygenic disease with a substantial genetic overlap with other mental illnesses (9). Environmental factors, such as stressful life events, particularly sexual and physical abuse, and emotional mistreatment, have been associated not only with BD onset, but also with the course of illness (10,11).

Compared to general population, individuals with BD have a reduced life expectancy of nearly 13 years, with around two to three times higher mortality rates compared to general population (12). This is due to natural causes, such as cardiovascular diseases, respiratory diseases and cancer, and also to the elevated risk of unnatural deaths, especially suicide (12), which can be 20 times more common than in general population

(13). Some risk factors for suicidal behavior include early onset, female gender, depressive polarity and comorbidity with personality or substance use disorders (13).

1.1.2. Types of affective episodes

1.1.2.1. Manic episodes

Manic episodes are characterized by significant changes in the individual's usual behavior, which affects social or occupational functioning and can require an acute hospital admission to prevent potential harm to oneself or others (14). During manic episodes, increased motor drive, expansive mood and behavior, irritability, increased self-esteem and reduced need for sleep are common (15). These symptoms need to be present most of the day, nearly every day for at least one week, or less if hospitalization is necessary (16). Psychotic symptoms (delusions or hallucinations) are present in about 75% of patients with an acute manic episode (15) and can be congruent with the mood state, with symptoms such as grandiosity, megalomanic or messianic ideation, or incongruent, with perceptions of self-referentiality or of being persecuted, among others (17).

1.1.2.2. Hypomanic episodes

Hypomania is a milder and shorter form of mania characterized by mild or moderate manic symptoms with a lower psychosocial impact compared to mania and not accompanied by psychotic symptoms. Hypomania does not affect functioning in a severe manner, does not cause severe social or occupational impairment and does not require hospitalization (18). The diagnosis of hypomania requires the presence of affective symptoms for at least four consecutive days (17).

1.1.2.3. Depressive episodes

Depressive episodes are characterized by low mood, decreased energy, anhedonia, psychomotor slowing, social withdrawal and low self-esteem, among others, for at least two weeks, with a significant functional impairment (15). Specifically, bipolar depression is typically characterized by hypersomnia, psychomotor inhibition, emotional lability and apathy (19), and appears earlier than unipolar depression. Psychotic symptoms can

occur during depressive episodes and can be mood-congruent, such as thoughts of guilt, uselessness, hypochondria, catastrophe or ruin, or mood-incongruent. In contrast with manic states, depressive episodes are not necessary for diagnosing BD. Depressive symptoms are associated with a significant functional impairment and reduced quality of life, somatic comorbidities and suicidal behavior (20,21).

1.1.2.4. Mixed episodes

Mixed episodes are characterized by the presence of symptoms from both depressive and manic poles simultaneously. In previous editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), the mixed specifier was used for those episodes in which the diagnostic criteria for both depressive and manic episodes were met, limiting this feature to BD I. However, the DSM, 5th Edition (DSM-5), introduced the mixed specifier to define either manic, hypomanic or depressive episodes when at least three criteria from the opposite affective pole coexist (16,17). This modification allows to better specify certain affective episodes, with is crucial given that mixed episodes have been associated with a more severe prognosis, a higher number of episodes, increased deaths by suicide and comorbidities (17).

1.1.3. Diagnostic classification

For the diagnosis of BD, the two main diagnostic criteria systems used are the *International Classification of Diseases*, 11th Edition (ICD-11) by the World Health Organization (WHO) (22), and the DSM-5, by the American Psychiatric Association (APA) (16). The following classification is based on DSM-5 diagnostic criteria. Mood patterns and BD subtypes are represented in **Figure 1**.

1.1.3.1. Bipolar disorder type I

In BD type I (BD I), at least the presence of one current or previous manic episode is required, whereas history of hypomanic and depressive episodes is not necessary to establish this diagnosis. The history of depressive episodes is not necessary for the diagnosis of BD I. However, throughout the course of illness, most patients typically experience hypomanic and major depressive episodes besides manic episodes (16).

1.1.3.2. Bipolar disorder type II

In BD type II (BD II), at least one current or previous hypomanic episode is required, added to the history of at least one major depressive episode (16). This diagnostic category typically includes individuals with history of depressive episodes that alternate with one or more hypomanic episode, with no history of manic episodes (16). Compared to BD I, patients with BD II usually suffer from higher recurrence rates and proportion of time in depression, and shorter periods of euthymia (23).

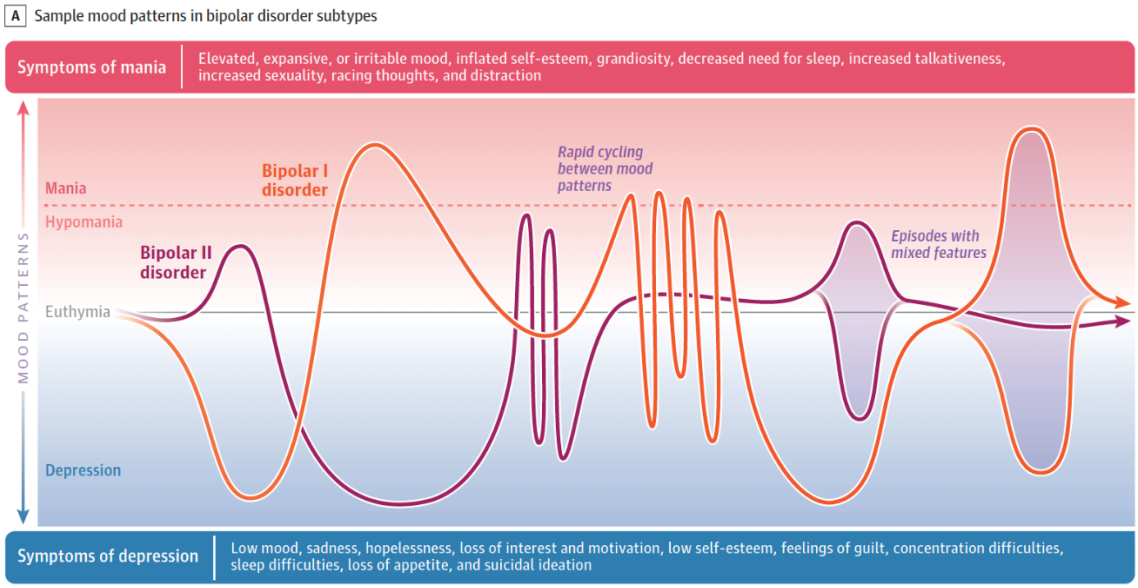


Figure 1. The figure illustrates the heterogeneity in frequency and duration of mood episodes in bipolar disorder. The figure is adapted from the published article "Diagnosis and Treatment of Bipolar Disorder" (24).

1.1.4. Treatment

Treatment of BD is recommended to be lifelong, since it is a chronic and highly recurrent disease, even when it is correctly diagnosed and treated. However, depending on the state of the illness, recommendations regarding it management vary. During depressive, mixed, manic or hypomanic episodes, treatment is focused on the remission of the current episode, whereas during euthymia treatment aims at preventing future relapses (15). Even maintaining continuous pharmacological treatment, 75% of patients with BD experience relapses within the first five years (25). Enhancing adherence and preventing pharmacological adverse events is one of the cornerstones in the management of

individuals with BD. In this section, evidence about acute and maintenance treatment, based on the available clinical guidelines, is described (3,26).

1.1.4.1. Treatment of acute mania

Despite non-pharmacological treatments can be used in some cases of acute mania, its treatment is mainly pharmacological. The same treatment approach is recommended in the management of hypomanic episodes. The combination of a mood stabilizer and an antipsychotic is recommended, since it appears to be more effective than monotherapy (3). However, the antimanic effect of antipsychotics is observed earlier than with mood stabilizers (27). Lithium is recommended as a first-line treatment, but others, such as valproic acid or carbamazepine, are also recommended. Considering side effects profiles and clinical efficacy of antipsychotics, the most recommended for the treatment of acute manic phases are aripiprazole, quetiapine, risperidone and olanzapine (14). Electroconvulsive therapy (ECT) is also effective in the treatment of acute mania, but is often reserved for refractory mania or cases with aggressive behavior. Some evidence has also shown efficacy of repetitive transcranial magnetic stimulation of the right prefrontal cortex (1).

1.1.4.2. Treatment of acute depression

Overall, patients with BD spend more time in depression than in mania or hypomania. However, the number of approved medications for bipolar depression is limited, which makes off-label or combination therapies usual in its management. Low antipsychotic doses are recommended as first-line treatment, although some of them are associated with weight gain and alteration of the metabolic profiles, which should be addressed routinely (15). Some evidence supports the use of anticonvulsants, olanzapine monotherapy, combined lithium and lamotrigine, and quetiapine and lamotrigine combination. Lurasidone, cariprazine and esketamine have also shown beneficial results in bipolar depression (15,28,29). The use of antidepressants in bipolar depression is controverted due to their risk of mood switching to hypomanic, manic or mixed episodes. They are not recommended in monotherapy, especially in BD I. Before their introduction, a mood stabilizer should be started first, and potential manic or hypomanic symptoms should be monitored closely. Among non-pharmacological treatments, repetitive transcranial magnetic stimulation, deep brain stimulation, vagus nerve stimulation,

lifestyle interventions and psychotherapy have shown efficacy. In addition, ECT has shown efficacy for treatment-refractory depression (15).

1.1.4.3. Maintenance treatment

Considering the recurrent and chronic nature of BD, long-term treatment aimed at preventing future relapses is recommended. Some of the preventive strategies include pharmacological treatment, psychological therapies and lifestyle interventions. With regard to pharmacotherapy, the use of a mood stabilizer alone or in combination with an antipsychotic is recommended (15). Pharmacological maintenance treatment usually depends on the patient's predominant polarity, defined as the pole at which a patient has at least twice as many episodes as at the other pole. However, a considerable proportion of patients have an undetermined predominant polarity (30). Thus, predominant polarity might guide pharmacological treatment with some exceptions, such as lithium, which remains one of the most effective drugs for preventing both manic and depressive episodes (31). Patients with a depressive predominant polarity might have a better response to lamotrigine and might require antidepressants at some points, whereas individuals with a manic predominant polarity might respond better to antipsychotics, and lithium and quetiapine might be useful in both situations (15). Monotherapy with lithium and lithium-valproate combination are more effective in preventing recurrences in BD I (32). Despite its efficacy, lithium has been associated in the long term with declining kidney function and the development of hypothyroidism and hypercalcemia (31). Quetiapine in monotherapy and in combination with lithium or valproate has also demonstrated efficacy as maintenance treatments (33). Regarding non-pharmacological treatment, psychoeducation, cognitive-behavioral therapy, interpersonal social rhythm and family-focused therapies have shown efficacy to prevent relapses in BD (34,35). Lastly, cognitive remediation has demonstrated to improve global functioning in BD (36,37).

1.1.5. Course and prognosis

The natural history of BD includes periods of remission or euthymia, with a high likelihood of relapse, particularly if adherence to treatment is poor and in cases of comorbid substance use (17). Drug misuse is common in patients with a manic predominant polarity and BD I (38). Individuals with a depressive predominant polarity are more likely to attempt suicide, have a depressive onset, and have BD II (39). Depression is the most

prevalent mood state and is more common in BD II than BD I, and subsyndromal states are three times more common than full syndromal episodes (40,41). Factors described as predictors of manic relapse include initial mood-incongruent psychotic features, lower premorbid occupational status, and initial manic presentation, whereas predictors of depressive relapse are higher occupational status, initial mixed presentation, and the presence of medical or psychiatric comorbidity (42). While considered to have a more favorable prognosis than schizophrenia, persisting alterations of psychosocial functioning are common in BD (42). Although long-term symptomatic remission does not guarantee functional recovery, it has a favorable impact on overall prognosis (42).

Throughout the course of illness, BD has been associated with cognitive, functional and medical impairments. First of all, neurocognitive deficits have been observed across all mood states and even during euthymia (43). Cognitive impairments are associated with psychotic symptoms, prolonged episodes, a higher number of manic episodes, and subsyndromal depressive symptoms (44). Functional impairment is linked to the presence of cognitive dysfunction (17). Apart from cognition and functioning, physical health is also affected in patients with BD (45), with very high rates of medical comorbidity and mortality from natural and unnatural causes. The premature death rate among bipolar patients is estimated to be up to 2-3 times higher than that observed in the general population, with suicide being one of the main causes (46). Currently, BD is considered one of the most disabling illnesses both physically and psychologically (47). The mentioned factors suggest that treatment in BD should not be only focused on preventing relapses and treating acute episodes, but also on the amelioration or restorage for the functional and cognitive deterioration of patients, and the prevention and management of associated comorbidities.

1.1.6. Comorbid disorders

1.1.6.1. Psychiatric comorbid disorders

Psychiatric comorbidity is reported in 90% of patients with BD (48). Anxiety, impulse control and substance use disorders have been found to be two to three times more common in bipolar patients than in the general population (48). Psychiatric comorbidity is more common in patients with earlier onset of BD, more sever course, poorer treatment adherence and suicidal behavior. Substance use disorders need special

attention to ensure prompt and appropriate interventions, since they might lead to poorer psychosocial adjustment and impact negatively on the course of the bipolar illness (42,49). They are associated with delayed recovery from mood episodes, increased suicidality, functional impairment, decreased adherence to treatment and lower quality of life (48). People with alcohol use disorder are at four times greater risk of having BD and those with use of illicit drug have a five times greater risk than non-users (48,50). Cannabis use is associated with more time in affective episodes and rapid-cycling. Comorbid substance use disorder is usually associated with poor treatment adherence and poorer social functioning (51). Attention deficit/hyperactivity disorder (ADHD) and anxiety disorders appear to be common and predict a poorer course of BD (5,42). The first diagnosis is present in up to 47% of adult ADHD populations and has high rates of comorbidity with other psychiatric disorders (48,52). Comorbid anxiety has been associated with earlier age of the first depressive episode, higher frequency of depressive episodes, longer time to recovery form depression, shorter time to relapse, poor functioning and reduced quality of life (53). Eating disorders are particularly associated with the depressive phases of BD (54), and are also more prevalent in this illness, ranging from 6 to 27%, than in general population, with an estimated prevalence of 4 to 10% (48). Lastly, personality disorders are more prevalent in BD compared to general population, and can difficult management of BD. Psychiatric comorbidities usually interfere with the diagnosis and treatment of BD and are associated with poorer outcomes, such as increased disease morbidity and mortality, including suicide risk (15).

1.1.6.2. Non-psychiatric comorbid disorders

Non-psychiatric comorbidities are highly prevalent in patients with BD (55), especially cardiovascular diseases and metabolic syndrome (MetS), which also arise earlier than in general population. Individuals with BD have an almost two-fold risk of cardiovascular disease mortality compared to general population (56). Other common comorbidities are osteoporosis and other endocrine and cardiovascular disorders (15). Comorbid medical conditions are linked to a more severe course of their psychiatric illness, worse functioning, more complex psychiatric treatment, treatment resistance, recurrence and higher utilization of medical services (57). Several medications used in the treatment of BD contribute to the increased risk of medical comorbidities. Other factors are associated with this increased risk, such as genetic vulnerability and lifestyle factors, including smoking, lack of exercise an unhealthy diet. In this line, individuals with BD require

regular monitoring of weight, glycaemia, dyslipidemia, blood pressure, and thyroid, liver and kidney function (58,59). Physicians should also be aware of the potential risks of each psychotropic medication used. In case of adverse events, risk and benefits should be assessed in each case and alternative therapeutic strategies might be considered (17). Patients with severe mental illnesses, including BD, are also considered at high risk of malnutrition due to lifestyle habits, pharmacological treatments, and in some cases limited availability of healthy food, inadequate social support and low socio-economic status (60), which will be developed in the next sections.

Regarding metabolic conditions, BD are at increased risk of MetS (61,62). Type 2 diabetes mellitus occurs up to three times as often in BD patients as it does in the general population. In addition, obesity is highly prevalent, and glucose and lipids are frequently dysregulated (63). MetS was defined in 1998 by a WHO diabetes research group as a number of interrelated physiological, biochemical, clinical and metabolic factors that increase the risk of cardiovascular comorbidity, type 2 diabetes mellitus and all-cause mortality (64). The recent International Diabetes Federation (IDF) definition includes the presence of three or more of the following criteria: (1) waist circumference relative to population and country-specific definitions; (2) HDL cholesterol <40 mg/dL (<1.04 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women or on drug treatment for reduced HDL cholesterol; (3) triglycerides ≥150 mg/dL (≥1.7 mmol/L) or on drug treatment for elevated triglycerides; (4) ≥130 mmHg systolic or ≥85 mmHg diastolic pressure or on antihypertensive drug treatment in a patient with a history of hypertension, and (5) fasting glucose ≥100 mg/dL or on drug treatment for elevated glucose (65).

Thus, patients with BD have been considered at increased risk of MetS and also of a poor nutritional status, which could be prevented by a balanced diet with the proper proportion and composition of macronutrients and micronutrients (66). The relationship between metabolic risk factors and BD is not well understood yet. However, a chronic low-grade proinflammatory state has been described in BD (67), and hypotheses point at underlying immune dysfunctions added to a chronic inflammatory state as risk factors for developing both BD and MetS (68). Higher mean body mass index (BMI) and waist circumference have been described in BD population compared to healthy controls (51,52). Other evidence has shown higher levels of cardiometabolic risk indicators in patients with BD compared to controls, including waist-to-hip ratio, BMI and non-HDL cholesterol (53). The atherogenic coefficient, measured as non-HDL cholesterol/HDL

cholesterol, has also been found higher in patients with BD compared to healthy controls (54). In addition, treatment with valproate and antipsychotics, but not with lithium and lamotrigine, was associated with increased risk of diabetes mellitus in a nationwide study in patients with BD (55). Other evidence supports that some pharmacological treatments, especially second-generation antipsychotics, are associated with higher total cholesterol and triglycerides levels, weight gain and increased fasting glucose (56,57), which facilitates the development of MetS (69). Lifestyle habits also play a role in the increased risk of MetS, including the lack of regular physical activity and hypercaloric diet (70). However, even after considering the mentioned factors, the higher incidence of cardiovascular risk factors among patients with BD remains not fully explained, especially in patients not treated previously with psychotropic medications (68).

1.2. Role of nutritional and metabolic factors in bipolar disorder

1.2.1. Definition of malnutrition and clinical implications

Among both medical and surgical conditions, hospital malnutrition is one of the most prevalent syndromes, since it affects about 30–60% of patients (71). However, it is only identified in about 3 to 5% of hospitalized patients (71). Clinical malnutrition is defined as a state where the organism cannot meet its nutritional and metabolic requirements (71) and is a result of the lack of a proper nutrition, aging or specific diseases, with altered body composition, such as decreased fat free mass, which is a risk to impaired physical and mental function (72,73). A poor nutritional status negatively affects diagnosis, prognosis, and the clinical course of various acute or chronic diseases (74).

Different mechanisms can be involved in malnutrition, including reduced intake, and the metabolic stress caused by that or by the inflammatory state of different acute or chronic conditions or treatments. Response to stress speeds up the metabolism, with an increase in protein catabolism, which consumes our protein reserves, altering the function of different organs and the activity of our immune system (75).

Malnutrition is often underrecognized by physicians. It is more prevalent among individuals with a BMI <18.5 kg/m^2 than those >18.5 kg/m^2 (15). In patients with diagnosis of malnutrition, different clinical outcomes have been found to be more prevalent, such a longer hospitalizations and higher likelihood to receive parenteral nutrition (15).

1.2.1.1. Malnutrition in somatic disorders

Different studies on non-psychiatric populations have found an association between an increased risk of malnutrition and impaired clinical outcomes. Malnutrition at hospital admission has been associated with increased patient morbidity and mortality, longer hospitalizations and higher healthcare expenses (76–79). For instance, in patients with chronic obstructive pulmonary disease (COPD), a poor nutritional status has been associated with cachexia, sarcopenia, higher exacerbation hospitalization rate and weight loss, and the last has been found to be a prognostic factor of COPD (80).

Other studies have been focused on oncologic populations. The nutritional status showed a role in wound healing in patients being treated for head and neck cancer (81), with an inverse correlation between nutritional status and would healing efficacy. Poor nutritional status has also shown to increase mortality rates due to all causes in pancreatic cancer patients (82). In individuals with breast cancer, malnutrition was associated with poor disease-free survival and overall survival (83,84); the second was also observed in intrahepatic colangiocarcinoma patients (85).

In early-stage multiple system atrophy, diabetic patients and acute ischemic stroke, malnutrition has been associated with major disability, adverse outcomes and mortality (86,87). In a sample of patients with acute ischemic stroke followed up for one year, a poor nutritional status, but not BMI, had a significant effect on an increased risk of post-stroke depression (88). In individuals with multiple sclerosis, enhanced Mediterranean diet compliance was independently associated with reduced malnutrition rates and also reduced depressive symptoms, with lower rates of overweight and obesity, and also with a decreased incidence of disease disability, higher physical activity and improved quality of life (89).

1.2.1.2. Malnutrition in psychiatric disorders

People with severe mental illnesses are often in poor physical health, which is associated with higher mortality and reduced life expectancy compared to the general population. Although psychiatric population has been considered at risk of malnutrition, few studies have assessed the nutritional status of individuals with mental illnesses and its implications on somatic or psychiatric clinical outcomes (60).

A nutritional screening performed in a sample of psychotic and depressive patients with anthropometric, severity of symptoms and functioning assessments, obtention of personal and medical data, use of nutrition risk screening tools, and laboratory values, showed that 32% of the inpatients and 34% of the outpatients were at risk of malnutrition, which was associated with higher levels of psychiatric symptoms and lower levels of functioning, despite mean BMI was overweight in both groups (60). A different study found that 48% of the acute psychiatric inpatients were at risk of malnutrition, with nurses' judgments about the patients' nutritional status scarcely related to the nutritional risk scores (90). Thus, previous evidence is limited but suggests a high proportion of

individuals at high risk of malnutrition that might benefit from nutritional support during their psychiatric treatment (60).

However, to date, in the mental healthcare setting, since the nutritional assessment of individuals with severe mental illnesses have received little attention, no specific nutritional risk screening tools have been explored or recommended in this population. The acknowledgment of patients' nutritional status in BD might help elucidate its relationship with different factors, such as the illness by itself, lifestyle habits, pharmacological treatments and medical and psychiatric prognosis.

1.2.2. Screening and assessment of malnutrition

Assessing nutritional status allows clinicians to determine general health of a patient from a nutritional viewpoint, and detection of malnutrition allow the implementation of nutritional interventions and treat potential contributory factors (75). All hospitalized patients should undergo a nutritional screening at their admission. The infrastructure and resources available, added to the healthcare setting in which nutritional assessment must be performed, determine which method can be used. Different screening and assessment tools have been designed to determine patients' nutritional status. To establish a nutritional diagnosis, the patient's medical history, a physical examination including anthropometric measurements, biochemical analysis and functional tests are recommended (91).

1.2.2.1. Nutritional screening tools

Nutritional screening is defined by the *European Society for Clinical Nutrition and Metabolism* (ESPEN) as a process to identify an individual who is malnourished, or at risk of malnutrition, to determine if a detailed nutritional assessment is required (73). The most common used screening and assessment tools are mentioned in this section.

The *Malnutrition Universal Screening Test* (MUST), the *Mini Nutritional Assessment Short Form* (MNA-SF) and the *Nutritional Risk Screening 2002* (NRS-2002) tools determine different risk levels of malnutrition according to BMI, unintentional recent weight loss, and the presence of an acute disease plus a reduction in food intake (74,75). The last one also considers the presence of a bedridden status and dementia or depression (74,75). The *Nutritional Risk Index* (NRI) was designed to examine the

association between malnutrition and surgical outcomes and is based on albumin levels and percentage of weight loss, with abnormal parameters associated with higher complication and mortality rates (74). The *Geriatric Nutritional Risk Index* (GNRI) corresponds to a modification of the NRI adapted to elderly individuals and is used in critically ill patients. It is calculated from albumin levels and the ratio between weight and ideal body weight (74). The *Prognostic Nutritional Index* (PNI) total score is calculated from albumin levels and total lymphocyte count (74).

The *Controlling Nutritional Status* (CONUT) scoring system was proposed as a screening tool for hospitalized patients (74). It is calculated from serum albumin concentration, total peripheral lymphocyte count, and serum total cholesterol concentration. Based on the total score, the patients are classified as having normal (score 0–1), mild (2–4), moderate (5–8), or severe (9–12) risk of malnutrition (75). Some studies have associated CONUT score with in-hospital mortality, length of hospital stay, infection, nutritional support, length of rehabilitation, and independence in activity of daily living at discharge (92–94). Higher CONUT score has also been associated with hospitalization costs, and lower CONUT score with functional outcomes (95). This score has also been associated with long-term recurrent stroke and major cardiovascular events (96), and was an independent prognostic factor of mortality after a follow-up of 3 to 12 months (97). Compared to other screening tools, CONUT score appeared to be more useful for predicting functional outcomes at discharge or at three months (74).

1.2.2.2. Nutritional assessment tools

The objective of nutritional assessment consists of documenting the basic nutritional parameters, identifying risk factors and specific nutritional deficiencies, and also those factors that may influence the prescription or administration of nutritional support (75). According to ESPEN (73), the nutritional assessment provides the basis for the diagnosis of malnutrition according to a clinical, psychological, social, and nutritional history, and a clinical examination that includes information on weight, height, BMI, body composition, biochemical data, calorie, protein, fluid, and micronutrient needs (75). It differs from nutritional screening in the amount of data obtained by different means to reach a diagnosis of malnutrition and its degree or severity. Nutritional assessment can be used to evaluate changes in nutritional status and response to nutritional interventions (98). Clinical assessments include the identification of risk factors for malnutrition in patients'

medical history, such as situations in which energy requirements are increased, and also demographic, socioeconomic and lifestyle data, including physical activity (99). The clinical examination should be aimed at identifying muscle atrophy, loss of subcutaneous fat, and hydration status, edema and other signs that can guide to specific deficits. Dietary habits might guide towards the possibility of global or specific nutrient deficiencies (75). Long-term changes in body weight reveal changes in body mass, but do not provide data about body composition. Some related parameters are used, such as its relationship with ideal weight, percentage weight loss, with 5% or more associated with morbidity and mortality (100), and BMI. Low BMI (below 18.5 kg/m^2) has been correlated will mortality and complications, but is not a good marker of malnutrition by itself (100).

Body composition methods that describe body compartments, such as fat mass, muscle mass, or bone mineral mass, are more objective and precise than anthropometric methods. Midarm circumference (MAC) and triceps skinfold thickness (TSF) are parameters used in the assessment of fat mass (75). Other body composition methods used are: bioimpedance analysis, dual-energy X-ray absorptiometry, computed tomography, magnetic resonance imaging and densitometry (101). Functional examinations include muscle function tests, such as dynamometry and respiratory function through the measurement of peak flow and forced expiratory volume in the first second (FEV_1), which reflects respiratory muscle strength and is related to catabolism and protein loss, and immune function by the measurement of cellular response to intradermal agents (102,103).

Different laboratory parameters are used in the assessment of nutritional status. The most extensively studied nutritional parameter is serum albumin, since in acute situations behaves as a negative acute-phase reactant since. In inflammatory situations, its synthesis is reduced and its degradation increased. However, it is a good nutritional indicator in chronic malnutrition (104,105). Prealbumin is a good marker of malnutrition when there are no signs of inflammation, and it is useful in the follow-up after a nutritional intervention. Transferrin is another marker used in the nutritional assessment (106,107). Creatinine reflects kidney function and also correlates with muscle mass, since it is a metabolism product from creatine and can allow the identification of severe muscle depletion (75). Nitrogen balance provides information related to protein catabolism (75).

Other blood parameters, such as cholesterol and total lymphocytes, are also correlated with the severity of malnutrition (107).

Different specific tools have been designed for nutritional assessment, such as *Subjective Global Assessment* (SGA) tool, which is used in hospitalized patients and considers the patient's history, including weight loss, changes in food intake habits, gastrointestinal symptoms, functional capacity, a brief physical examination and the physician's overall assessment (108). The *Mini Nutritional Assessment* (MNA) is used in elderly patients and includes anthropometric measures, general evaluation, dietary assessment, and self-perception of health and nutritional status (75).

The ESPEN criteria include the minim consensus-based items for the diagnosis of malnutrition, with two options: (1) BMI <18.5 kg/m^2; (2) an involuntary weight loss of >10% indefinite of time, or >5% over the last 3 months, added to either BMI <20 kg/m^2 in adults or 22 kg/m^2 in the elderly, or a low fat-free mass index (FFMI) of <15 and 17 kg/m^2 in women and men, respectively (100). It was validated in hospitalized and outpatient individuals. The *American Society for Parenteral and Enteral Nutrition* (ASPEN) assessment tool includes six items: a reduction in intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized accumulation of liquids, and decreased muscle strength measured by dynamometry. If the patient has two or more of these items, the diagnosis of malnutrition is established (102). Finally, the *Global Leadership Initiative on Malnutrition* (GLIM) diagnostic criteria (109) require firstly the use of a validated screening tool and then the presence of at least one phenotypic criterion (involuntary weight loss >5% in the last 6 months, low BMI, or reduced muscle mass) and one etiological criterion (reduced food intake or assimilation and inflammation caused by disease) (75).

1.2.3. Nutritional and metabolic variables as prognostic factors in bipolar disorder

Previous evidence has shown that MetS and its related components are associated with worse psychiatric outcomes, including a chronic course of illness, rapid cycling and worse global and cognitive functioning (50). In BD, MetS has also been linked to increased hospitalization rates, poorer insight, and impaired executive function (110). Despite obesity is the most studied metabolic risk factor, it shows controversy with regard

to psychiatric outcomes. However, current evidence suggests that MetS, obesity and impaired glucose metabolism could be considered risk factors for worse course of illness (111). A recent longitudinal study demonstrated an association between higher BMI and higher prevalence of suicide attempts, medical comorbidities and a more severe psychiatric illness (74), which is supported by a previous study that reports lifetime suicide attempts in BD might be predicted by comorbidity with obesity, as well as by lower bilirubin serum levels, and with a trend toward statistical significance with higher total cholesterol serum levels (75). Moreover, obesity and BD have been both considered inflammatory conditions, and BMI seems to contribute to inflammation in BD. In turn, proinflammatory cytokines have been associated with higher rates of depressive relapse in 12 months (76) and with negative effects on cognition, along with cerebrovascular alterations (112).

MetS has been associated with changes in brain imaging, such as reduced frontotemporal thickness in overweight patients, widespread abnormalities in white matter structure in obese, dyslipidemic and diabetic patients, and reduced frontoparietal and subcortical volumes in individuals with impaired glucose metabolism (112). Increased BMI has been also associated with decreased white matter and temporal lobe volumes in early BD (113–115). Clinically significant weight gain has shown a link with greater volume loss in the left orbitofrontal cortex, left cingulate gyrus and left middle temporal gyrus. The last factor was identified as a predictive factor for more days depressed in BD (115).

Little evidence is available considering the impact of the nutritional status in patients with BD in short- or long-term prognostic factors. Results from a randomized clinical trial have shown effective outcomes after a lifestyle intervention in the improvement of BMI, waist circumference, anxiety, depressive symptoms and quality of life in severe mental illnesses (82). Regarding specific factors, reports from the Older Adults with Bipolar Disorder (OABD) task force showed that lower levels of vitamin B_{12} correlated strongly with memory loss and poor cognitive performance in psychotic bipolar depression (116), and that vitamin B_{12} and folate may influence on affect and cognition. Low serum concentrations of folate, but not of B_{12}, were also associated with brain white-matter disease and smaller hippocampus and amygdala brain-volumes (117). However, limited data is available assessing the impact of malnutrition on the illness course in BD (118).

1.3. Energy availability in bipolar disorder

1.3.1. Bipolar disorder as a biphasic condition

Acute episodes of BD are characterized by differences in energy availability, among other signs and symptoms. In mania and hypomania, the reduction of need for sleep, increased energy and increased motor drive are common. By contrast, during depressive episodes, a reduction of energy and spontaneous movements, psychomotor retardation and hypersomnia are often observed. Different studies have pointed to the role of mitochondrial function as a key factor involved in the pathogenesis and pathophysiology of BD (119–122).

Morris, Berk and cols. proposed in 2017 a model in which BD could be understood as a biphasic disorder of energy availability, increased in mania and decreased in depression (119). The core premise of this model suggests that the fluctuating symptoms seen in BD may be linked to a two-phase disruption in mitochondrial bioenergetics. It posits that mitochondrial dysfunction could act as a state-dependent marker of the disorder, with increased mitochondrial function typifying bipolar mania and reduced activity typifying bipolar depression (119,122).

1.3.2. Mitochondrial function

1.3.2.1. Mitochondria: structure and functions

Mitochondria are cellular organelles involved in several biological processes. They perform key biochemical functions essential for metabolic homeostasis, since they are involved in energy production, metabolism of reactive oxygen species (ROS), calcium homeostasis, regulation of apoptotic cell death, synaptic plasticity and neurogenesis, modulating neuronal activity and preventing neuronal damage (122). Mitochondria are present in practically all eukaryotic cells. The endosymbiotic theory proposes that mitochondria evolved from two prokaryotes that ended up in a symbiotic relationship. One bacterium was phagocytosed and became progressively specialized in producing energy through oxidative phosphorylation (OXPHOS), becoming a mitochondrion. Progressively mitochondria turned into plastic organelles, specialized in energy production, but they also developed apoptotic properties. Growing evidence suggests

that their apoptotic function is tightly linked to nutrient availability and respiratory efficiency (123).

The principal function of mitochondria is to generate energy in form of adenosine triphosphate (ATP) via oxidative metabolism of nutrients using two major steps, 1) oxidation of NADH or $FADH_2$ produced during the glycolysis, Krebs or tricarboxylic acid (TCA) cycle or β-oxidation of fatty acids, and 2) OXPHOS as a main source of ATP (124).

Mitochondria are plentiful within neuronal dendrites and synaptic terminals, playing a key role in brain functioning. Neurons, especially in grey matter, have a high number of synapses and mitochondria due to their elevated energy requirements and the inability to store it (125). The activity of mitochondria is essential for regulating neuronal activity, both short- and long-term neuronal plasticity, cellular resilience, and behavioral adaptations, primarily through their influence on long-term potentiation (126–128). To match the local energy needs in neurons, mitochondria constantly move along microtubes networks, changing mitochondrial trafficking, distribution, anchoring, and membrane dynamics (129). Maintaining a balance between energy supply and demand, as well as preserving mitochondrial health, is critical for cellular homeostasis and ensuring proper neuronal function (122).

Mitochondria contain their own DNA, called mitochondrial DNA (mtDNA), which contains 37 genes that encode 13 proteins, 22 tRNA, and 2 rRNAs. Each mitochondrion contains 800 to 1000 copies of mtDNA, which are maternally inherited (124). Whereas genes from mtDNA encode 13 protein subunits of the electron transport chain (ETC), nuclear DNA (nDNA) code the rest of the mitochondrial proteins (130). In contrast to nDNA, mtDNA is vulnerable to DNA damage secondarily to constant exposure to ROS (131).

Mitochondria are composed of two highly specialized membranes, the mitochondrial outer membrane (MOM) and the inner membrane (MIM). These membranes define two separate mitochondrial compartments: the mitochondrial matrix and the intermembrane space (123). The mitochondrial matrix contains different enzymes that participate in the TCA cycle and are responsible for the generation of NADH and $FADH_2$ (132), which act as electron donors and are required for the generation of ATP through OXPHOS via the ETC, present within the folds on the MIM (133–135). The MOM and the intermembrane

space are relatively more permeable than the MIM; the last contains enzymes involved in the process of ETC and ATP generation via OXPHOS.

1.3.2.2. Oxidative phosphorylation (OXPHOS)

The ETC is localized within the MIM (133–135) and is composed of five multimeric protein complexes (I-IV and ATP-synthase or complex V). These complexes are responsible for ATP production by OXPHOS. This process is performed by means of electron flow between the first four complexes; the electrons donated by NADH and $FADH_2$ and transferred to components of the ETC. This transfer of electrons along the ETC is coupled with the transport of protons from the mitochondrial matrix into the intermembrane space through sequential redox reactions that finally reduce O_2 into H_2O in complex IV (124). Finally, ATP synthase uses the energy accumulated in the proton gradient to phosphorylate adenosine diphosphate (ADP) into ATP (136). The ETC function is represented in **Figure 2**.

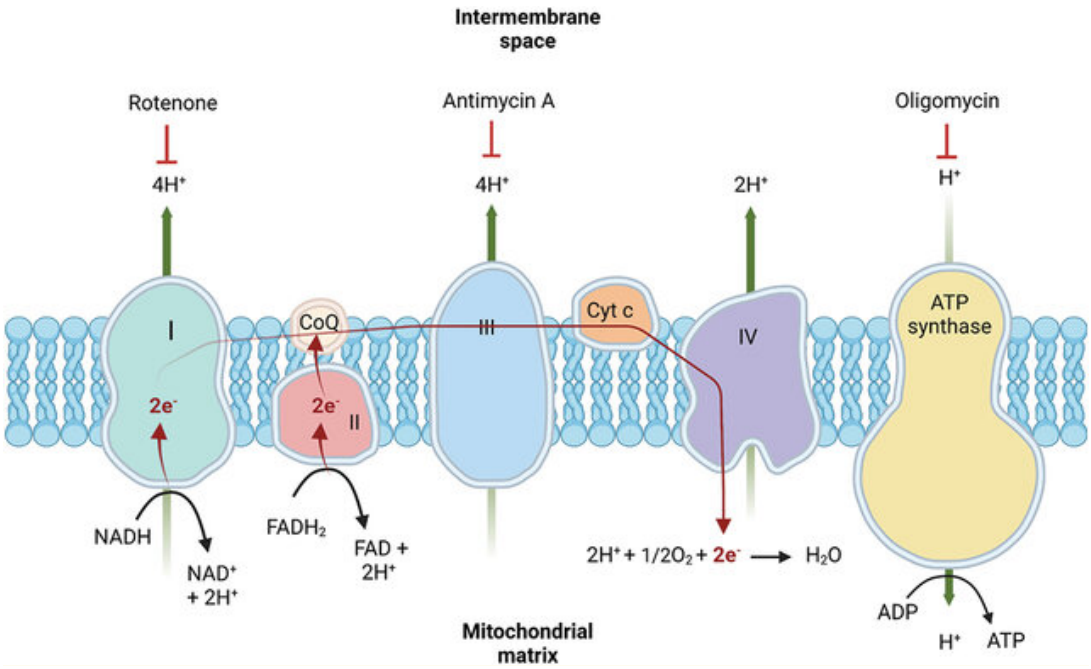


Figure 2. The figure shows the structure of the electron transport chain (ETC) in the internal mitochondrial membrane. Mitochondrial function can be measured through the use of specific molecules - oligomycin, rotenone and antimycin - to isolate different parts of the ETC. The figure is obtained from the published article "Cold stored platelets in the management of bleeding: is it about bioenergetics?" (137).

1.3.2.3. *Oxidative stress*

Since an electrochemical proton gradient is generated for ATP production during OXPHOS, which is an imperfect process, electrons can escape and produce a single-electron reduction of O_2, forming superoxides and other ROS (138,139). The overproduction of ROS has been associated with oxidative damage inflicted on mitochondrial proteins/enzymes, lipids and membranes, and DNA, which leads to the interruption of ATP generation and other essential functions in mitochondria (124), such as synaptic plasticity (140). The ETC also generates other reactive species such as nitric oxide (NO) and reactive nitrogen species (RNS), which affects cellular proteins. Cells have many ways to counter the effects of oxidative damage, either by directly diminishing the generation of free radicals or by scavenging the free radicals by antioxidants (124).

Cellular defense mechanisms that alleviate the oxidative stress is based on antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) and glutathione peroxidase (GPx). Other non-enzymatic defenses that protect cells against oxidative stress include vitamins E and C, glutathione (GSH), various carotenoids and flavonoids (122).

When the antioxidant defenses are insufficient, oxidative damage in mitochondria is produced (141), which affects ETC function and leads to decreased ATP production, mitochondrial dysfunction, reduced mitochondrial biogenesis and pathologic conditions such as aging, metabolic diseases and neurodegenerative disorders (142–144). In the last decades, part of the literature has been destinated to understand the implications of mitochondria in different pathological processes, including MetS and mood disorders (124).

1.3.2.4. *Other mitochondrial functions*

Apart from the neutralization of ROS by antioxidant defenses, mitochondria possess other mechanisms to maintain cellular homeostasis, such as mitochondrial dynamics, biogenesis, and mitophagy (145).

Mitochondria also play an important role in regulating the process of apoptosis through both intrinsic and extrinsic pathways, which allows in the brain the removement of those

neurons and glia that are functionally impaired or unable to make neuronal connections (146). In the intrinsic mitochondrial-mediated pathway, cellular stress signals, such as high levels of intracellular Ca^{2+} or ROS, as well as the activation of proapoptotic proteins (i.e., Bcl-2 family members) in the MOM (147), trigger a cascade of processes that activate caspases. This results in cleavage of several proteins, DNA fragmentation and cell death (148,149). In the extrinsic pathway, activation of cell surface death receptors enhances processes that alter membrane permeability, resulting in leakage of proapoptotic factors and apoptosis (123,148).

Moreover, mitochondria regulate calcium homeostasis, a key factor involving aerobic metabolism and one of the apoptosis triggering factors (150,151). At the same time, calcium is a secondary messenger involved in the regulation of neurotransmission and neuroplasticity in the brain (130). The MOM is permeable to calcium, and the MIM contains uniporters for its inward movement, and Na^{+}/Ca^{2+} and Ca^{2+}/H^{+} antiporters for its outward movement (152). Mitochondria also form signaling hubs with the endoplasmic reticulum through the mitochondria-associated membranes (MAMs), which allows the regulation of lipid synthesis and rapid transmission of calcium signals between these two organelles (152). Mitochondrial calcium concentrations increase in cases of high cytosolic calcium levels and in situations of ATP demand, and decrease when cytosolic levels are low, or the ATP/ADP ratio is high. Calcium can modulate OXPHOS by direct binding, enhancing post-transcriptional modification, and by the activity of a calcium-dependent binding protein. It also binds to complex IV and reduces ATP inhibition of this enzyme.

ATP synthesis is also enhanced by stimulation of the aspartate-glutamate carriers and the ATP-Mg/Pi (i.e., calcium-binding mitochondrial carrier protein, SCaMC-3) transporters on the MIM. In addition, calcium leads to increased NADH synthesis and higher production of pyruvate (153). However, when calcium levels are excessive in the intracellular space or mitochondria, they induce stress and excitotoxicity, ATP synthesis is reduced (154,155), and calcium is ejected through the Na^{+}/Ca^{2+} exchanger and the mitochondrial permeability transition pore (mPTP). Impairment in the control of mPTP function has been associated to the mitophagy of depolarized mitochondria, induction of apoptosis, and necrosis (130). At the same time, calcium homeostasis is regulated by different proteins, enzymes, and cellular signaling networks, which may be risk pathways for mood disorders when they are altered (122,156).

The oxidation of fatty acids to acyl-CoA, a process called β-oxidation, takes place in the mitochondrial matrix, and allows the obtention of NADH and $FADH_2$, necessary for OXPHOS. The acetyl-CoA resulting from this process can enter the TCA cycle and get oxidized, coupled to the production of reducing power (157). Alterations in these metabolic processes have been associated with metabolic conditions, such as heart failure, diabetes mellitus or MetS (158–160).

High energy requirements activate mitochondrial biogenesis. Mitochondrial activities depend not only on the abundance of these organelles, but also their morphology, and mitochondrial dynamics (161–163). Mitochondria are permanently fusing and fissioning with each other, and damaged mitochondria are rapidly eliminated, which allows mitochondrial networks to meet metabolic demands (161,164). The loss of fusion and fission abilities results in altered mitochondrial populations (158).

Mitochondria are also involved in synaptic plasticity, related to the effects of glutamate and BDNF. The last factor enhances mitochondrial respiration and ATP production through different mechanisms, such as increased glucose transport, upregulation of the mitochondrial biogenesis, and enhancement of respiratory efficiency (165,166). ATP synthesis is necessary for the mobilization of synaptic vesicles to the active sites of synapse in neurons. When ATP production is reduced, neuronal transmission is consequently impaired (167,168). Finally, mitochondria also play a key role in neurogenesis, the process of neural stem cell proliferation and differentiation into new neurons through the mitochondrial genome and specific proteins (122).

The functions mentioned above are closely related, affecting one each other, rarely having isolated effects, which explains that, in pathological conditions, several mitochondrial functions are impaired.

1.3.3. Interplay between nutritional, metabolic factors and mitochondrial function

The current global dietary patterns have been linked to the substantial increase in the prevalence of metabolic and cardiovascular diseases. Therefore, the establishment of healthy dietary patterns is a global priority to reduce the onset of nutritional deficiencies, metabolic and cardiovascular disorders (158). Even though the way nutrients promote

our health is not fully known, since they trigger a multitude of effects, they need to be metabolized by mitochondria to obtain energy. The availability of nutrients might have been the primary evolutionary factor influencing opposite mitochondrial functions: generating energy for life sustenance and releasing apoptotic proteins to induce cell death in conditions where nutrients are limiting, acting as a sensor of nutrient availability (158). Thus, mitochondrial function is key to understand how dietary patterns and nutrients influence mitochondrial function (158).

Caloric restriction, understood as reduced food intake without malnutrition, is regarded as one of the most successful approaches to prolong lifespan, with some processes related to mitochondrial function, such as reduced ROS production (123). On the contrary, excess food intake might impair respiratory capacity and susceptibility to apoptosis, with metabolic consequences such as insulin resistance (123). In this section, the link between nutrition, metabolic disorders and mitochondrial function are explored (123).

1.3.3.1. Malnutrition

Nutrients are needed by mitochondria to obtain energy, since mitochondria is the metabolic center for carbohydrate, protein and lipid metabolism (169). A balanced diet is important to compensate extreme conditions and ensure bioenergetic functions and mitochondrial activity (158). Variations in protein content from the diet affects mitochondrial count and alters activities of numerous mitochondrial enzymes. Changes in carbohydrate components of the diet have a large effect on enzymes involved in energy metabolism, especially those related to triglyceride synthesis, and can affect mitochondrial function through changes in phospholipid composition (170). When mitochondrial cholesterol levels are increased, fluidity of the MIM is decreased (171–173), which affects the function of specific membrane carriers and the transport of fatty acids, carboxylic acids, amino acids, cofactors, inorganic ions and nucleotides across the MIM (174). It also alters the inward transport of GSH, which affects oxidative stress and the detoxification reactive species and can impair mitochondrial activity (175).

Several vitamin and mineral deficiencies can also result in aberrant expression of mitochondrial proteins and have a deleterious effect on mitochondrial structure, biogenesis and function (170). When identified, these situations can be reversed by

nutrient repletion, which may be useful to support mitochondrial function in stressful conditions (176).

1.3.3.2. *Metabolic syndrome*

Converging evidence from post-mortem brain tissue, genetics, brain imaging and lactate studies suggests that altered mitochondrial functioning and oxidative stress increase the risk of presenting MetS or its components, cardiovascular diseases, and also age-related neurodegenerative diseases (177,178). Excessive ROS, diet and microbiota alterations and altered mitochondrial-related gene expression can contribute to the shift in bioenergetics from aerobic to anaerobic respiration. This shift causes cells to be reliant on glycolysis for energy production, causing a build-up in lactate, which can act in competition with glucose as a fuel source and affect glucose uptake. This is implicated in the emergence of MetS and may lead to the development of insulin resistance (179–181), often found in patients with BD (182). Metabolic markers, such as elevated lactate, sharpen focus on mitochondrial pathways as pivotal in the genesis and progression of mood disorders (197).

MetS has also been associated with reduced mitochondrial biogenesis, leading to variations in mitochondrial number and altered membrane potential, which entails defective energy production, and accumulation of ROS in cells and tissues (169). Increased glucose levels enhance ROS overproduction, which leads to morphological changes in mitochondria (179). Aging, altered mitochondrial biogenesis and decreased antioxidant defense capacity along with genetic factors have shown to predispose to insulin resistance, which is the major cause of many metabolic diseases (169).

Oxidative stress leads to reduced lipid oxidation and increased cellular lipid accumulation; this situation inhibits insulin signaling (183–185). Inhibition of insulin signaling pathway has shown to facilitate the accumulation of lipids and free fatty acids and contribute to hypertriglyceridemia (186), which is responsible for the increase of visceral adiposity and of waist circumference (187). Fat redistribution is accompanied by an increase of proinflammatory molecules, especially interleukin-6 (IL-6), tumor necrosis factor (TNF), or C reactive protein, secreted by macrophages, causing a low-grade chronic inflammation state (188,189). Abdominal obesity has been correlated with increased levels of oxidative stress biomarkers (190,191) and altered mitochondrial

biogenesis, oxidative metabolism, mitochondrial gene expression and reduced ATP production (192,193). Such mitochondrial impairments, increased oxidative stress, and low-grade chronic inflammation influence the development of hypertension (194,195). Oxidative stress also facilitates the formation and progression of the atheroma plaque responsible of cardiovascular events, as observed in patients with MetS (158). Concurrently, damaged mitochondrial structures result in release of mtDNA, known as circulating cell free mitochondrial DNA (ccf-mtDNA) to the periphery. Ccf-mtDNA is recognized as damage-associated molecular patterns (DAMPs). This aberrant mitochondrial DNA outside the mitochondria triggers the toll-like receptor 9 (TLR9) signaling cascade, amplifying NFκβ-mediated proinflammatory gene expression and the activation of the NLRP3 inflammasome, culminating in chronic low-grade inflammation (196).

Acetyl-CoA is produced in the mitochondria from pyruvate, fatty acids or amino acids, and is crucial for initiating cholesterol synthesis, which highlights the relationship between mitochondrial function and lipid metabolism. In cases of impaired mitochondrial function, cells might shift from oxidative glucose metabolism to anaerobic glycolysis, which is less efficient and results in lactate production. This situation means a reduced cell capacity to oxidize glucose and increased fatty acid oxidation, which contributes to excessive acetyl-CoA production, altering the generation of metabolites in the TCA cycle and leading to elevated ROS production (179,181).

1.3.3.3. Mitochondrial nutrients

Diet quality also significantly impacts MetS, since a poor quality of diet, characterized by high processed food, refined carbs, and low fruit, vegetable, whole grain, and fish intake, is tied to depression, obesity, and cardiometabolic disorders (197). Increased simple carbohydrates intake versus isoflavone-rich foods were correlated with a greater occurrence of MetS, and diets with high fat or sugar content might promote an increase in the ETC activity and then lead to the overproduction of mitochondrial ROS (158,198). Increasing evidence now suggests that targeting mitochondria with specific nutrients could efficiently prevent and ameliorate various conditions associated with mitochondrial dysfunction. Those nutrients could act either directly in specific mitochondrial pathways or indirectly by enhancing the expression of genes encoding mitochondrial proteins (170). Some nutrients have demonstrated to serve as alternative energy sources, enhance mitochondrial antioxidant defense system, have anti-inflammatory effects,

induce mitochondrial biogenesis or act as cofactors in biochemical processes to improve mitochondrial function (170).

Some of the nutrients associated with an enhanced mitochondrial activity are monounsaturated fatty acids, obtained from extra virgin olive oil, and polyunsaturated fatty acids (omega-3 and omega-6 fatty acids). Vitamins are essential micronutrients for the proper function of mitochondrial metabolism, especially vitamins B, C, A, D, E. However, in excess, they might be harmful. An excess of vitamin A intake (199) promotes oxidative stress and mitochondrial death (200) and is associated with an increased likelihood of MetS (201), and a high intake of vitamin B_3 (niacin), can result in niacin-induced insulin resistance (202). When Vitamin C and E are consumed in excess, they promote oxidative activity instead of antioxidant function (203). Trace elements, including cupper, manganese, iron, selenium or zinc, are essential for the proper mitochondrial function. Polyphenols, mostly found in plant-based food (204), and are categorized as flavonoids and non-flavonoids (205). They have antioxidant properties, enhance mitochondrial biogenesis and glucose metabolism and are associated with low lactate levels (197). The influence of nutrients on mitochondrial function is shown in **Figure 3**.

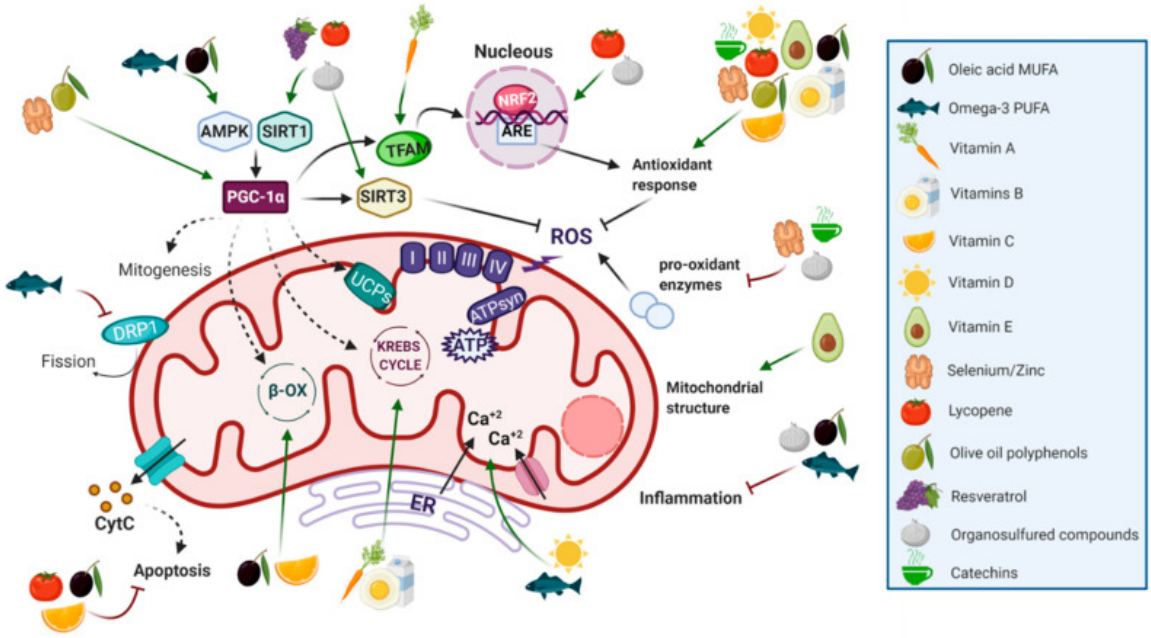


Figure 3. This image illustrates the main nutrients with beneficial effects on mitochondrial function. Nutrients activate numerous pathways; among them, different nutrients activate PGC-1α signaling, which promotes mitochondrial biogenesis, β-oxidation, glucose utilization, and antioxidant detoxification. Figure obtained from "Nutrition, Bioenergetics, and Metabolic Syndrome" (158).

Oleic acid (present in vegetable oils), omega-3, selenium, zinc, polyphenols, carotenoids, and the organosulfur compounds (found in vegetables) activate a great number of pathways, including PGC1α signaling, a main gene regulator of energy metabolism. The activation of the PGC1α promotes mitochondrial biogenesis, β-oxidation, glucose utilization, uncoupling, and antioxidant detoxification. Vitamin C and oleic acid are necessary for β-oxidation. One of the main effects of oleic acid, carotenoids, organosulfur compounds, vitamins B, C, D, selenium, and zinc, and olive oil polyphenols in our cells is the decrease of oxidative stress by the promotion of antioxidant response and also the inhibition of pro-oxidant enzymes. Vitamin E also acts as an antioxidant and enhances the maintenance of a correct mitochondrial structure, while omega-3 inhibits mitochondrial fission. Omega-3 and vitamin D are involved in calcium homeostasis. Vitamin C, lycopene, and oleic acid have shown to inhibit apoptosis, while oleic acid, omega-3, and organosulfur compounds to reduce inflammation (161).

Creatine, synthesized endogenously by the liver, kidney and pancreas and obtained exogenously from the diet acts as an energy-boosting compound by increasing creatine/phosphocreatine stores and preventing ATP depletion (170). It enhances fatty acids β-oxidation and mitochondrial enzymes activity, increases antioxidant effects and improves mitochondrial function (124).

Coenzyme Q_{10} (CoQ_{10}) or ubiquinone is a bioactive lipid that acts as an electron carrier from complexes I and II to complex III in the ETC. In its reduced form (ubiquinol), CoQ_{10} has antioxidant properties and protects mitochondrial lipids, proteins and DNA from oxidative damage, and also has antiapoptotic and anti-inflammatory effects (170). Alpha-lipoic acid (α-LA) is a coenzyme present naturally in mitochondria involved in energy metabolism. Its reduced form, dihydrolipoic acid, is a powerful antioxidant that has shown in animal studies to decrease oxidative damage, reduce oxidant formation and improve mitochondrial function (170). *N*-acetylcysteine (NAC) has also shown antioxidant properties, since it increases the glutathione pool and its related enzymatic antioxidant system (122).

1.3.4. Mitochondrial dysfunction in bipolar disorder

Mitochondrial dysfunction and impaired energy metabolism has been suggested in BD (119,206), which might have implications in severity and disease progression (207,208).

Altered mitochondrial function can arise from various factors, including alterations in the expression of genes related to mitochondria, in mitochondrial biogenesis, structural abnormalities, fluctuations in OXPHOS, and shifts in metabolite levels (209). Some evidence supports the hypothesis that mitochondrial dysfunction has a contribution in BD, particularly in mood and cognition (210,211), with a biphasic pattern of energy availability according to the mood state (119). Evidence on mitochondrial dysfunction in BD is represented in **Figure 4.**

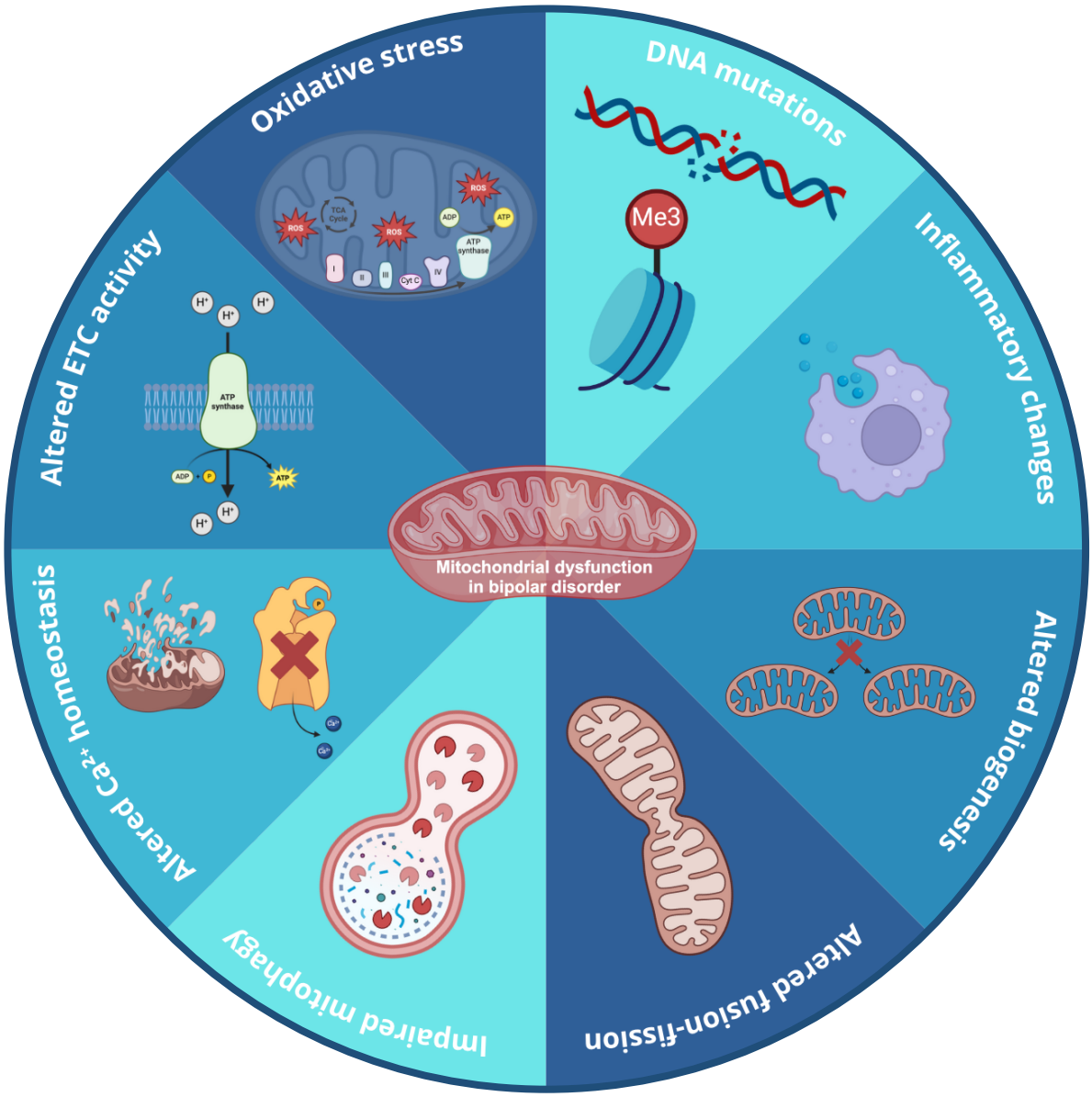


Figure 4. This image shows the main mitochondrial functions altered in individuals with bipolar disorder. Figure created by the author.

1.3.4.1. Mitochondrial bioenergetics

The brain is the organ with the highest energy consumption, but it is enabled to store glycogen and depends on OXPHOS for energy production, which explains a great quantity of mitochondria in it. Since a high amount of ATP is produced in the brain, ROS and RNS production is also abundant, making this organ vulnerable to oxidative damage, which occurs when the oxidative load exceeds antioxidant capacity (125).

1.3.4.2. Metabolic changes

Neuroimaging studies and analysis of postmortem brain tissue from individuals with BD revealed a decreased number of neuronal and glial cells and reduced brain volume in prefrontal and limbic regions. These findings have been associated with a reduction of oxidative bioenergetic production, favoring anaerobic glycolysis, and subsequently impaired neuroplasticity, phospholipid metabolism and calcium regulation. Furthermore, variations in neurometabolites, including high-energy compounds, have been observed in mood disorder patients, such as lower levels of phosphocreatine (PCr). Changes in N-acetyl-aspartate (NAA), ADP, and ATP levels have been also reported in BD and associated with mitochondrial dysfunction (212,213).

Additionally, some studies have identified enzymatic abnormalities in creatine kinase (CK), which catalyzes the production of ATP from ADP and PCr in cases of high-energy demand, and downregulation of CK in postmortem BD brains (214,215). This hypothesis aligns with previous findings indicating that individuals with BD can maintain average brain concentrations of high-energy compounds at rest, but exhibit underlying abnormalities when energy demand is higher (214). Other evidence shows an increase in lactate and taurine levels and decreased brain intracellular pH, which suggests a shift from OXPHOS to glycolysis as a primary energy source in BD. Increased lactate, particularly during manic phases, in various brain regions (frontal cortex, caudate, cingulate cortex) suggests either heightened ATP demand or defective oxidative metabolism (119).

1.3.4.3. Electron transport chain (ETC)

Numerous studies examining postmortem brain tissue, skeletal muscle, or blood samples have demonstrated alterations in enzymatic activities associated with the TCA

cycle and ETC in individuals with BD, added to impaired mitochondrial oxygen consumption. Different mitochondria-related genes have been found to be downregulated in BD compared to controls (169). For example, some studies have documented decreased expression of certain complex I subunits, and others have also reported decreased activity (209,216,217). Other research has shown decreased activities of citrate synthase, a key enzyme in the TCA cycle, and also complexes II and IV, along with increased complex I activity and complex I/citrate synthase ratio in blood platelets of BD patients during depressive episodes. Other consistent findings revealed in isolated mitochondria from peripheral blood mononuclear cells (PBMCs) a decrease only in complex II activity in bipolar depressed patients (218). Other evidence shows no significant differences in ETC activity in mood disorders (219,220). However, the evidence is limited, and no studies have assessed intra-individual differences in ETC activity according to different mood states.

A review aimed at compiling data on proteomic analyses of postmortem brains collected from patients affected by BD identified 95 proteins as altered, most of them related to the TCA cycle and the ETC, and others with the antioxidant enzymes, which might contribute to a better understanding of the impaired metabolic mechanisms in BD (221).

1.3.4.4. Oxidative damage

Different studies have reported an increase in ROS production and reduced antioxidant capacity in BD. Increased lipid peroxidation products in the cingulate cortex (206) and increased markers of oxidative and nitrosative damage in the prefrontal cortex (222,223) have been described. Results from a meta-analysis assessing oxidative stress markers in individuals with BD showed an increase of markers of lipid peroxidation, DNA/RNA damage and nitric oxide (224).

The antioxidant system has been also studied in postmortem brains of individuals with BD, with lower expression of SOD, microsomal glutathione S-transferase and GPx in frontal areas, and lower expression of the last one in the hippocampus (177,225), as well as reduced activity of SOD and catalase in these patients (226,227). Some evidence shows increased SOD activity during manic and depressive episodes (226,228,229); other authors reported decreased SOD levels during manic episodes (230). Results on euthymic bipolar patients are controverted, with some showing increased SOD levels (228) and others decreased activity (226,231). Also in euthymia, increased activity of

GPx was found in BD patients, but not in acute mood episodes (199). By contrast, other evidence reported increased GPx levels in bipolar depression compared to healthy controls (232), and others did not find significant differences between healthy controls and different mood states (223,226). Research involving chronic patients has indicated either decreased or unchanged catalase activity (227,231). In contrast to these findings, elevation in catalase levels were reported in bipolar depression, as supported by earlier studies (232). Furthermore, compared to controls, decreased GSH levels were observed among patients in the late stages of BD (223).

1.3.4.5. Calcium homeostasis

Reduced ATP production leads to an impairment in mitochondrial and cellular functions by altering mitochondrial membrane potential, diminishing calcium uptake capacity. Studies on BD brains reveal altered intracellular calcium levels, especially heightened during manic states (156,233), alongside gene expression changes in calcium-related signaling pathways. Excessive calcium affects both neuronal excitability and signaling cascades that regulate gene expression, disrupting neuronal processes, such as dendrite development, synaptic plasticity, and excitatory/inhibitory balance (234).

Calcium/Calmodulin Dependent Protein Kinase Kinase 2 (CaMKK2) plays a pivotal role in neuronal calcium-calmodulin signaling, regulating mitochondrial function and energy balance via AMP-activated protein kinase (AMPK) and PGC1α activation (235). Mutations affecting CaMKK2 function are linked to BD (236), leading to reduced CaMKK2 activity and decreased BDNF expression (237,238).

1.3.4.6. Mitochondrial morphology

Changes in mitochondrial morphology, distribution, and degradation have also been described in BD. In both prefrontal neurons from postmortem brain samples and in peripheral cells, obtained from individuals with BD, a larger number of smaller-sized mitochondria was found (239,240). Also, an abnormal pattern of clumping with marginalization in the intracellular distribution of mitochondria in peripheral cells was observed, along with atypically shaped mitochondria (240). Moreover, in iPSC-derived hippocampal dentate gyrus-like neurons from patients with BD (209), smaller mitochondria were found compared to healthy controls. Altered fusion and fission processes, which can alter mitochondrial size, were also reported (240). In line with these

findings, a downregulation of the mitochondrial fusion-related proteins Mfn-2 and Opa-1 and an upregulation of the fission protein Fis-1 were observed in PBMCs from BD patients (241).

1.3.4.7. Mitochondrial degradation and apoptosis

Patients with BD have shown in their PBMCs a downregulation of mitophagy-related proteins, added to a NLRP3-inflammasome activation, which means an imbalance in mitochondrial fission and fusion processes favoring fission and heightened caspase-3 levels (241,242). This indicates a potential overload of damaged mitochondria and a shift towards apoptosis as the predominant pathway to mitigate tissue damage in BD (243,244). Indeed, upregulation of apoptotic genes such as *FAS*, *BAK*, and *APAF-1* has been observed in the hippocampus of BD patients (225), while downregulation of the antiapoptotic protein Bcl-2, due to various polymorphisms, exacerbates calcium dysregulation. Additionally, endoplasmic reticulum stress response is evident across all phases of BD, particularly in mania (243).

Moreover, the PI3K/Akt pathway activates mTOR, stimulating OXPHOS (119). Being crucial for cell survival and proliferation, it exhibits upregulated transcription in mania, activated by oxidative stress and IL-6, and regulated by AMPK, indicating its potential involvement in mania (225). Akt promotes mitochondrial survival by inhibiting cytochrome c release into the cytosol, which is the final step of mitochondrial apoptosis (245).

GSK-3α and GSK-3β are activated under chronic oxidative stress conditions like BD, with more pronounced activation in mania than depression, and their inhibition correlates with clinical improvement (119). GSK-3 activation promotes cellular apoptosis via Fas receptor activation, also enhanced by TNF-α, which paradoxically has a neuroprotective role. In mania, TNF-α activation of GSK-3 promotes neuronal survival by upregulating NFκβ, which inhibits TNF-α mediated apoptosis, inhibits OXPHOS and promotes aerobic glycolysis. TNF-α inhibits mitochondrial biogenesis, which is compensated by increased SIRT-1 activity (119). SIRT-1 is involved in the regulation of glucose and lipid metabolism, through insulin signaling, and protects the cells against inflammation and oxidative stress. It activates PGC1α, thus promoting glucose uptake and mitochondrial biogenesis (126). Compared to bipolar depression and healthy controls, manic patients have shown increased levels of NFκβ and SIRT-1 (119). SIRT-1 levels are decreased in

bipolar depression compared to euthymia, and TNF-α levels seem to be lower in depression than in mania (119). NFκβ also leads to elevated cytoplasmic CREB levels in BD patients, which is significant given CREB's role in mediating BDNF's antioxidative effects, with lower levels observed in mania compared to depression and in BD patients compared to controls (246). Additionally, CREB involvement in neurogenesis has been found diminished in depression (247).

1.3.4.8. Inflammatory changes

A proinflammatory environment has been described in all phases of BD, with an increase in cytokine levels, especially IL-1β, IL-6, and TNF-α, and increased nitric oxide in brain and plasma. These changes have been found to be greatest in mania, and also higher in bipolar depression compared to unipolar depression (125).

1.3.4.9. Genetic changes

Genetic evidence further points to the involvement of mitochondrial dysfunction in BD. Some studies indicate that individuals with mitochondrial diseases frequently develop psychiatric symptoms, particularly mood symptoms (247).

Genome-wide association studies (GWASs) have pinpointed multiple loci associated with BD susceptibility, including *CACNA1C*, *ANK3*, *ODZ4*, *SYNE1*, and *TRANK1* (248,249), albeit with relatively modest effect sizes. Furthermore, the potential involvement of *de novo* protein-altering mutations and calcium-related genes were reported in BD pathogenesis and were associated with earlier disease onset (250,251). While no direct mutations in mitochondrial mtDNA have been linked to BD (235), certain mtDNA haplogroups display altered cerebellar pH akin to that observed in BD cases. Moreover, specific mtDNA variants, such as a rare gene variant, 3644T>C, appear to be more prevalent in BD patients compared to healthy controls (252,253).

Studies examining postmortem brain tissues reveal mixed findings regarding mtDNA alterations in BD. While some report an increased prevalence of mtDNA deletions (254,255), others fail to replicate these results (256). Regarding mtDNA copy number, meta-analyses in BD exhibit variability, with some showing reduced copy numbers in patients, particularly during mood episodes (257). Notably, decreased mtDNA copy

number and accelerated epigenetic aging in the hippocampus of BD patients was described in a meta-analysis (258). Moreover, fluctuations in mtDNA copy numbers correlate with the severity of mood symptoms during depressive and manic episodes (259).

Overall, these genetic and molecular findings underscore the intricate interplay between mitochondrial dysfunction and BD, shedding light on potential avenues for novel therapeutic interventions.

1.3.4.10. Other changes in mitochondrial function

The purinergic system appears dysregulated in patients with BD (260) and involves increased activity in oxidative stress-related pathways like SIRT-1, AMPK, PKA, PKC, GSK, and inositol triphosphate, as well as increased levels of antiapoptotic proteins such as Bcl-2, PI3K, mTOR, Akt, and uric acid. Their activation drive OXPHOS, leading to elevated oxidative stress. Uric acid levels, increased in all phases of BD but particularly in mania, facilitate greater mitochondrial function by enhancing calcium uptake, increased membrane potential, and ATP production (261), with lower levels being linked to mood disorder risk. Uric acid also scavenges peroxynitrite, which has high mitotoxic activity (125) and has other neuroprotective effects, including increased AMPK activity and adaptative responses to oxidative stress.

Furthermore, cAMP and PKA seem to be upregulated in BD, which enhances OXPHOS via phosphorylation of proteins involved in ATP synthesis, such as cytochrome c oxidase, bolstering mitochondrial protection. Cytochrome c oxidase, the terminal respiratory enzyme, is a metabolic marker for neuronal functional activity (262); depressive symptoms have been associated with its alterations.

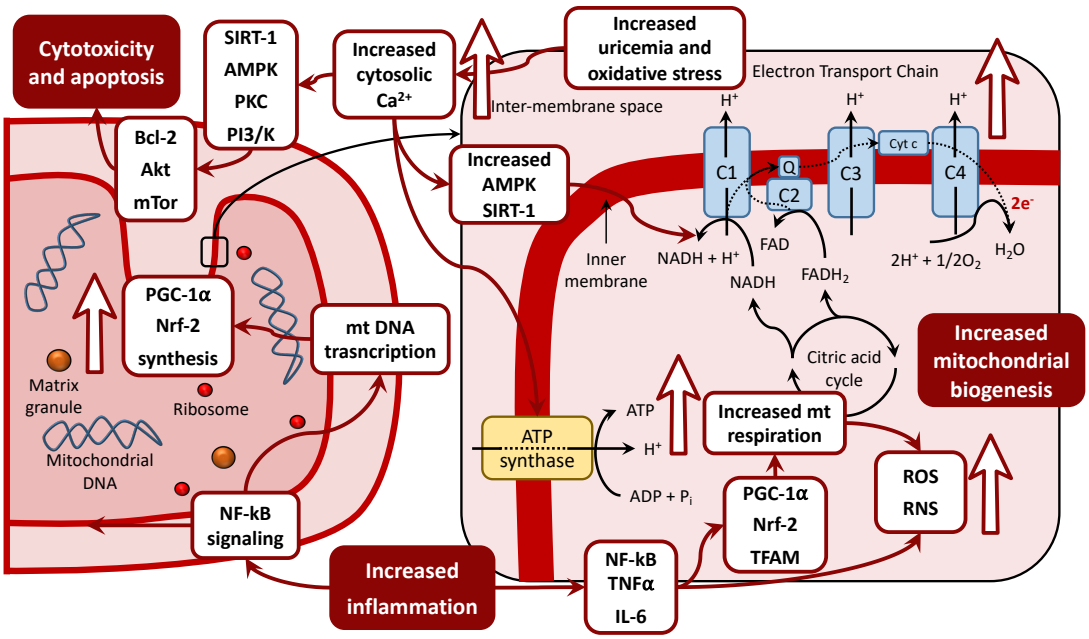
CREB activity, crucial for ETC enzyme complex transcription, which also upregulates CK, is altered in BD, affecting neuroprotection and energy production (119). Genetic variations in the purinergic system and cAMP signaling genes have been identified in BD, which underscores the influence of these pathways on circadian clock genes and ATP production, particularly notable in manic episodes. Increased activity of antiapoptotic proteins, enzymes and signaling cascades has been found in mania, which enhances mitochondrial activity (119). Polymorphisms in clock genes, able to modify

cellular sensitivity to oxidative stress or genotoxic insults, have been associated with increased risk for developing severe forms of BD. These genes control circadian NAD+ concentrations, which increase SIRT-1 and SIRT-3 activities, and this stimulates OXPHOS. Both NAD+ and SIRT-1 directly activate ATP synthesis and upregulate circadian genes, suggesting a pathway of influence in mood disorders (125).

Regarding the hypothalamic-pituitary-adrenal (HPA) axis, depression correlates with HPA hyperactivity due to corticosteroid receptor-mediated feedback impairment, leading to elevated glucocorticoid levels and increased mitochondrial activity (122,125). Glucocorticoids inhibit apoptosis by forming a complex with the antiapoptotic protein Bcl-2 to inhibit the formation of Bax-containing pores on the MOM. They also reduce the release of calcium and cytochrome c from the mitochondria, which inhibits apoptosis (247). However, chronic elevation can induce neuronal toxicity, ETC dysfunction, excessive ROS generation, apoptosis, and cell death (263).

In terms of neurotransmitters, glutamate dysregulation is implicated in mood disorders, with elevated levels in mania and reduced glutamine-to-glutamate ratios in depression. Oxidative and nitrosative stress have been associated with higher dopamine transmission and impaired dopamine transporter (DAT) function in mania (264). However, dopamine and uric acid levels act in a synergistic way to repair oxidative damage (119). Dopamine can protect neurons against glutamate-induced excitotoxicity and confer anti-apoptotic effects. Thus, high dopamine and glutamate levels together with high uric acid levels may not exert the expected detrimental effects, and pro-apoptotic signals may induce the expression of anti-apoptotic genes and stimulate OXPHOS (119). Findings in mitochondrial function according to acute states are summarized in **Figure 5**.

5A



5B

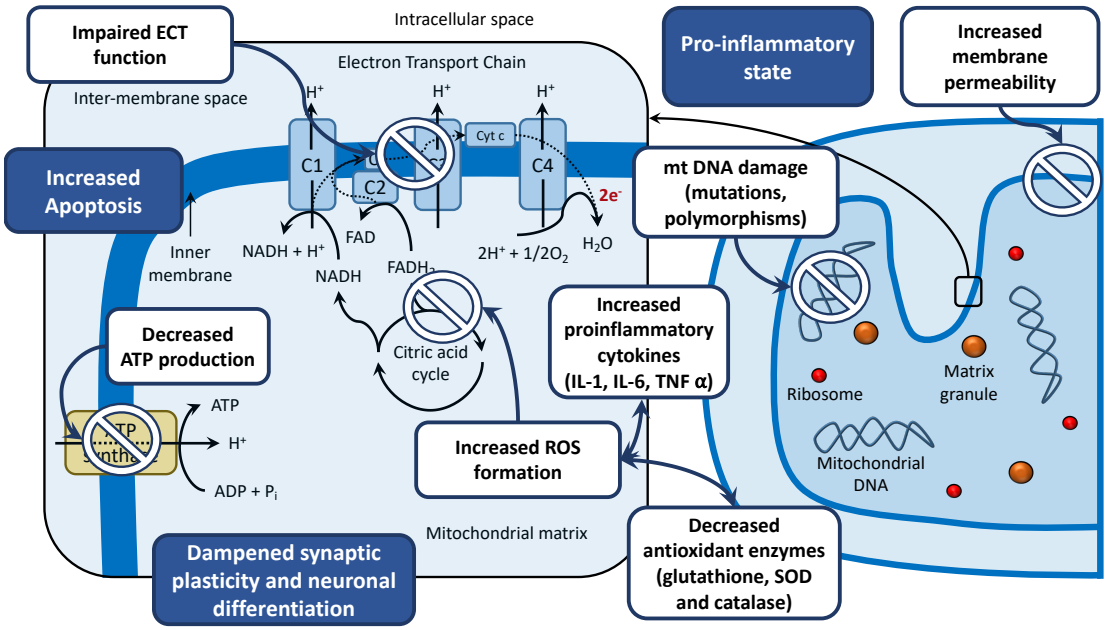


Figure 5. The biphasic mitochondrial model in bipolar disorders, with mitochondrial dysfunction observed in manic (5A) and depressive episodes (5B). Figure adapted from "The Role of Mitochondria in Mood Disorders: From Physiology to Pathophysiology and to Treatment" (122).

1.3.5. Other bioenergetic changes in bipolar disorder

Other bioenergetic changes have been described in BD. Different studies have assessed both lactate and pH levels in BD as markers of the same underlying process, specifically, the shift from aerobic to anaerobic metabolism for ATP production. Nevertheless, the physiological influence of mitochondrial dysfunction on aerobic capacity and cardiopulmonary functioning in BD is still unknown, and studies on this area are scarce. The available evidence on the mentioned biomarkers is summarized below.

1.3.5.1. Exercise tolerance

The impact of exercise on mitochondrial function, which plays a pivotal role in determining exercise capacity, has been investigated in various contexts (265,266). Indeed, structured exercise regimens have shown a beneficial effect on metabolism and mitochondrial function.

Reduced aerobic endurance and muscle strength are linked to diminished physical function, heightened susceptibility to lifestyle-related conditions, and premature death (267). Within BD, prolonged illness duration, elevated BMI, increased levels of depression, and reduced physical activity are correlated with poorer physical fitness, highlighting a prominent modifiable risk factor for somatic comorbidities (268). The assessment of cardiorespiratory fitness, typically measured by maximum oxygen uptake (VO_2peak), serves as a predictive marker for cardiovascular disease and premature mortality. However, research in BD remains limited, despite indications of mitochondrial dysfunction as a potential hallmark in the disorder's pathophysiology (265,269).

In youth with BD, aerobic capacity was assessed with a 20-minute bout of aerobic exercise on a recumbent cycle ergometer, which revealed that female sex, higher perceived exertion during exercise and non-caucasian race were significantly associated with lower subjective exercise tolerance. Lifetime use of any psychotropic medication was associated with lower exercise tolerance in females, but not in males (269).

Other evidence in euthymic BD patients and healthy controls that measured physical exercise, pulmonary function and the rate of oxygen consumption at baseline and during exercise in a treadmill showed briefer exercise duration for BD subjects than in controls.

However, baseline and exercise respiratory parameters, including maximal oxygen uptake, forced vital capacity, forced expiratory volume, and maximal ventilation, did not differ significantly between bipolar subjects and controls (265). To date, no studies have explored the association between respiratory capacity and mitochondrial function in BD.

1.3.5.2. Lactate

Results from a systematic review assessing lactate from magnetic resonance studies showed that five of six studies reported increased lactate levels in patients with BD compared to healthy controls (270). The sixth study (271) compared lactate levels during manic and euthymic periods and showed no difference during mania but decreased brain lactate levels during euthymia compared to controls. Two of the studies (272,273) did not find a correlation between lactate levels and mood state. Lactate levels did not seem to correlate with symptom severity, mood state or disease type (BD type I or II). In most studies, lactate was measured in the anterior cingulate cortex (274). A different systematic review with meta-analysis review including 12 studies using either through proton echo-planar spectroscopy, magnetic resonance spectroscopy or cerebrospinal fluid lactate showed in seven of them significantly elevated lactate levels in BD compared to healthy controls. This meta-analysis suggests a tendency to anaerobic energy production in neurons and astrocytes and a shift from pyruvate to lactate, potentially due to decreased mitochondrial ETC activity (275,276).

1.3.5.3. pH

A systematic review including 13 magnetic resonance studies assessing brain pH in bipolar patients, most of them with only euthymic participants, showed in the majority decreased pH compared to healthy controls (274). In most studies, pH was measured in the frontal lobe. However, a follow-up study (277) examined patients during a manic episode and also when they became euthymic, and showed that pH in mania was similar to that of the control group, whereas pH during euthymia decreased compared to both pH of controls and pH during manic episode. Another follow-up study (278) examined BD patients at depression and euthymia, and found decreased pH while they were euthymic but not depressed. Medication and symptoms severity did not seem to alter

significantly pH levels. These results highlight the importance of providing evidence assessing bioenergetic functions in different states of the illness.

Results from a meta-analysis that included 10 studies assessing postmortem pH levels in individuals with psychiatric disorders showed that brain pH was significantly lower in patients with BD than in control participants, even after considering potential confounding factors (279).

1.3.6. Potential interventions targeting bioenergetic functions

Conventional psychotropic drugs for mood disorders, such as mood stabilizers, antidepressants, and antipsychotics, have demonstrated to influence on mitochondrial functions. Thus, some evidence suggests that mitochondrial dysfunction and oxidative stress may be therapeutic targets of mood stabilizers, since they have demonstrated neuroprotective effects when oxidative stress is induced in animal models (280,281). Lithium has shown to reduce apoptosis, to enhance neuroprotection and neurotrophism, and to prevent excessive mitochondrial calcium influx. As observed with valproate, lithium has demonstrated to reduce oxidative stress and confer antioxidant effects (122). Antidepressants have been found to increase mitochondrial biogenesis and enhance antioxidative capacity against oxidative stress (282,283). Some antipsychotics have also shown to reduce oxidative stress (122).

Over the last years, a number of agents have been studied or developed as potential therapeutic factors to treat and improve the course of mood disorders, including mitochondrial modulators (284), which have been studied with the aim of enhancing antioxidant defenses or mitochondrial functioning as adjuvant therapy to antidepressants (284,285). Vitamin D has been reported to regulate mitochondrial oxygen consumption and dynamics, and its deficiency has shown to decrease oxygen consumption rate in mitochondria (286,287). The potential benefits of vitamin D supplementation among patients with BD have been suggested, since it has been associated with a reduction in both depressive and manic symptoms. However, the role that vitamin D plays in the cognitive and clinical characteristics of BD is still unclear (286,287).

Other dietary supplements (or nutraceuticals) assessed as potential treatments in mood disorders (288) include NAC, alphalipoic acid, acetyl-L-carnitine, S-adenosylmethionine,

CoQ10, carnosine, creatine monohydrate, and melatonin, with some positive results in small samples (118). Other studies have demonstrated modulatory effects of omega-3 fatty acids on mitochondria (289,290).

Regarding dietary patterns, the Mediterranean diet was associated with antioxidative properties and antidepressant effects in a randomized clinical trial (291). Results from animal studies suggest that caloric restriction seems to predispose to higher mitochondrial efficiency but also to high-fat induced oxidative damage (292). Other evidence shows that the ketogenic diet, characterized by a low-carbohydrate diet, upregulates mitochondrial antioxidant status and protects mtDNA from oxidative damage (293–295). It has been suggested as a potential adjunctive therapy. This diet changes the energetic source of the organism (294,296), which switches from glucose to breakdown of fatty acids. Despite data on mood disorders is limited, early reports support the hypothesis about its potential beneficial effects on mood stabilization (297).

Finally, physical activity has been related to increased mitochondrial biogenesis, increased mitochondrial content and oxygen utilization capabilities, and aerobic exercise ameliorates loss of skeletal muscle mitochondrial content (298,299). Despite evidence on BD is still scarce, results from a network meta-analysis indicated antidepressant effects of exercise (300).

2. HYPOTHESES

Primary hypothesis: in BD, a biphasic pattern of energy production will be observed, which is increased in mania and reduced in bipolar depression, compared to euthymia, and this can be measured through immediate markers of respiratory function, such as maximal oxygen uptake (**study III**), and also from cellular samples through the measurement of CTE activity (**study II**).

Secondary hypotheses:

1. Differences in mitochondrial function patterns will be observed in acute mood episodes (depressive or manic) compared to euthymia, and also when comparing euthymic patients with healthy controls. Specifically, from the measurement of oxygen consumption capacity from polymorphonuclear cells (PBMCs), oxygen consumption capacity will be increased in mania and decreased in depression compared to euthymia and healthy controls (**study II**).
2. Variations in aerobic capacity will be observed through determined measurements in respiratory function in patients during an acute mood episode (depressive or manic) compared to euthymia, and this will reflect an increased tendency to anaerobic respiration during mania compared to depressive episodes and euthymia (**study III**).
3. A positive correlation between aerobic capacity and mitochondrial respiratory capacity will be observed in patients with BD during both acute mood episodes and euthymia (**study III**).
4. Patients admitted to an acute psychiatric ward, and especially those with BD, will have nutritional and metabolic impairments that will be associated with the short-term course of their psychiatric illness, measured by hospital length of stay (**study I**), and in the long-term, with an association with the severity of their disease, including the number of readmissions in the following years (**study IV**).
5. A predictive model based on the assessment of nutritional parameters with a machine-learning algorithm will be useful to predict a poor nutritional status and long-term prognosis in patients with BD (**study IV**).

3. OBJECTIVES

Primary objective: to assess and determine biomarkers related with bioenergetic parameters, including aerobic respiratory capacity and mitochondrial oxygen consumption capacity, to identify intra-individual differences in BD between manic and depressive episodes and symptomatic remission, defined as a substantial improvement in *Hamilton Depression Rating Scale* (HDRS) or *Young Mania Rating Scale* (YMRS) scores in the same individuals to reduce the bias caused by inter-individual variability (**studies II** and **III**).

Secondary objectives:

1. To compare differences in the oxygen consumption capacity of mitochondrial CTE between acute mood episodes and healthy controls (**study II**).
2. To identify the correlation between CTE mitochondrial respiratory capacity and aerobic capacity during physical activity, across different states of the illness (**study III**).
3. To determine longitudinally differences in the aerobic capacity and oxygen uptake between the acute mood episodes and clinical remission (**study III**).
4. To explore whether aerobic respiratory capacity could serve as a potential state-dependent biomarker of mitochondrial dysfunction in patients with BD (**studies II** and **III**).
5. Tu study the influence of BMI and physical activity on aerobic capacity in acute states of BD and clinical remission (**study III**).
6. To characterize the nutritional profile of patients admitted to an acute psychiatric ward, with a special focus on BD (**studies I** and **IV**).
7. To determine whether a deficient nutritional status is correlated with impaired clinical outcomes, such as the length of stay during an acute hospitalization (**study I**).
8. To identify specific nutritional and metabolic variables that might better predict a poor nutritional status in patients admitted to an acute psychiatric ward, especially individuals with BD (**studies I** and **IV**).
9. To evaluate in hospitalized patients with BD and an acute manic episode the relationship between nutritional status and psychiatric prognosis, including the number of emergency visits, acute readmissions and time to relapse during a three-year follow-up period (**study IV**).

10. To identify nutritional factors associated with hospital readmission in three years in patients with BD and an acute manic episode, and the potential of nutritional variables to predict malnutrition and readmission in BD through the use of a machine learning algorithm (**study IV**).

4. MATERIAL, METHODS AND RESULTS

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Effects of malnutrition on length of stay in patients hospitalized in an acute psychiatric ward

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Abstract

Introduction: Psychiatric patients are considered at risk for malnutrition due to pharmacological treatments, lifestyle habits and the mental illness by itself. Even though metabolic risk factors have been related to worse outcomes in certain conditions, the evidence regarding the nutritional status and its impact on the length of stay in psychiatric inpatients is scarce. This study aims to characterize the nutritional status in acute psychiatric patients, to correlate it with the length of stay, and to find specific potential indicators of malnutrition.

Methods: Adult patients admitted to the Hospital Clínic of Barcelona acute psychiatric ward throughout a 1-year period were included in this cross-sectional study. Sociodemographic and clinical variables were registered, including length of stay and the nutritional status measured with the CONUT score.

Results: Malnutrition was observed in 42.5% of patients. Plasmatic transferrin saturation, protein and iron levels were inversely correlated with length of stay, having low iron levels an association with longer hospitalizations. The length of stay was not influenced by diagnosis or treatment. Negative correlations with

the nutritional status were found in: BMI, cholesterol, triglycerides, albumin, total proteins, prealbumin, iron, lymphocytes and zinc levels, and transferrin saturation. The multivariate analysis showed a significant association for cholesterol and zinc levels, lymphocyte count, and BMI.

Conclusions: Our results suggest that nutritional status might influence the course of psychiatric admissions. Cholesterol and zinc levels, lymphocyte count, and BMI might be factors strongly associated with malnutrition. This consideration might allow the identification of profiles in which lifestyle interventions could be implemented.

KEYWORDS

acute unit, CONUT, malnutrition, nutritional status, psychiatric disorders

1 | INTRODUCTION

Hospital malnutrition is a highly prevalent problem that affects up to 50% of both medical and surgical patients.[1,2] Clinical malnutrition can be defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition, such as decreased fat free mass, and body cell mass leading to diminished physical and mental function and impaired clinical outcomes.[3] Indeed, some studies have shown that a poor nutritional status at admission is associated with increased patient morbidity and mortality, resulting in longer hospital stays and increased healthcare costs.[1,2,4,5] In patients with psychiatric disorders there are some variables that might be considered risk factors for a poor nutritional status, such as pharmacological treatment side effects, lifestyle habits as inactivity, poor diet, and the illness by itself, depending on the phases of the disease. For example, during depressive phases patients can present reduced appetite and weight loss.[6] There are also other barriers for an adequate diet, such as limited availability of healthy food, inadequate social support, a low socio-economic status, or a limited budget among others.[7,8] Despite this, little data are available on malnutrition in psychiatric populations except for studies related to eating disorders.[9] Another limitation is the lack of malnutrition risk screening tools for people with mental disorders.[10] However, there is an increasing interest to study the nutritional status in patients with severe mental disorders,[11,12] given the important burden that diet, lifestyle factors, and their consequences, may have in this population where physical health is often compromised, presenting a higher prevalence of cardiovascular diseases and a reduced life expectancy compared to the general population.[6,13,14]

So far, various studies have reported nutritional status as a prognostic marker in a number of diseases. In order to assess the nutritional status, some studies use the controlling nutritional status score (CONUT), which takes into account the total lymphocyte count, serum albumin, and total cholesterol levels. This tool has shown an inverse correlation with prognosis in several solid tumors, hematological malignancies, and heart diseases.[15–18] Despite the available data, the studies performed in this field do not include psychiatric population, being psychiatric patients often excluded from the studies or not considered among the reference population.[4,5,19,20]

Some studies have reported metabolic disturbances are related to worse psychiatric outcomes. For instance,

Significant outcomes

- Malnutrition was observed in 42.5% of inpatients admitted to our acute psychiatric unit.
- Plasmatic transferrin saturation, protein and iron levels were inversely correlated with length of stay, having low iron levels an association with longer hospitalizations.
- Negative correlations with the nutritional status were found especially for cholesterol and zinc levels, lymphocyte count, and BMI.

Limitations

- There is a lack of previous evidence about the global nutritional status of psychiatric inpatients, with the exception of patients with eating disorders.
- The cross-sectional design of this study cannot reveal causal dynamics between variables.

metabolic syndrome, obesity, and impaired glucose metabolism have been considered risk factors for worse outcomes in patients with bipolar disorder, since they have been related to a chronic course of the illness, worse global functioning, and rapid cycling.[21]

During acute psychiatric hospitalizations, clinical practice tends to include the assessment of different analytical parameters, including cholesterol, total protein levels, and lymphocyte count. Nevertheless, to the best of our knowledge, there is a lack of evidence regarding the impact of the nutritional status in psychiatric inpatients on the length of stay, medical comorbidities, and other prognostic factors.

Considering the missing data on psychiatric population, this study aims to provide a first approach to evaluate whether a deficient nutritional status is correlated with specific outcomes, such as the length of stay in an acute hospitalization unit. Secondary aims of this study include the characterization of the nutritional status in patients admitted to an acute psychiatric ward, the correlation between different nutritional variables and the assessment of specific nutritional variables that might better predict a poor nutritional status in this population.

2 | MATERIALS AND METHODS

2.1 | Participants

The data analyzed derived from records corresponding to patients aged 18 years or older admitted to the Hospital Clínic of Barcelona acute psychiatric ward. The records included a 1-year period. Ethical approval was provided by the Hospital Clínic Research Ethics Committee (protocol code: D2017).

Patients from which no metabolic parameters were available at the beginning of the hospitalization were excluded from the study. Patients with more than one admission in the same year were included only once, considering the first admission. No restrictive criteria were established in terms of diagnosis, being all patients admitted in the acute psychiatric ward considered for inclusion.

2.2 | Variables assessment

2.2.1 | Sociodemographic and clinical measures

Some of the variables collected for analysis included age, gender, length of stay, the presence of medical conditions and primary and secondary diagnoses. Variables regarding treatment included use of benzodiazepines, antipsychotics, antidepressants, mood stabilizers or electroconvulsive therapy (ECT) during the admission.

2.2.2 | Nutritional measures

The nutritional status was assessed at admission with the CONUT score, which takes into account the total lymphocyte count, serum albumin, and total cholesterol levels. Total scores between 0 and 1 were considered normal, 2–4 mild malnutrition, 5–8 moderate malnutrition, and 9–12 severe malnutrition.[16]

Other metabolic variables included body mass index and triglycerides, proteins, transferrin, prealbumin, iron, zinc, and transferrin saturation.

2.3 | Statistical analyses

In the descriptive analysis, quantitative variables were expressed by mean and standard deviation (SD), or median and interquartile range (IQR). Results from categorical variables were shown as frequencies (number and percentage).

T-test and Mann Whitney *U* tests were used for mean comparisons between two groups, using *t*-test for data that were normally distributed. Chi-square tests were used for the comparison of categorical variables, and Fisher exact tests were performed when the expected cells were lower than five.

For the correlation of nutritional parameters with length of stay or nutritional status and for the identification of predictive parameters, linear regression was used after correlation analyses. To calculate the association of malnutrition with nutritional parameters, psychiatric diagnosis, sociodemographic characteristics and pharmacological treatment, logistic binary regression analyses were conducted.

Aiming to predict the influence in the length of stay of blood parameters or nutritional status logistic regression analyses were used. Univariate logistic regression models were conducted for each of the potential associated factors. A p-value <0.05 was used for the screening covariates. Forward stepwise selection algorithms were used for selecting the covariates in the multivariate logistic regression model. At each step, the least significant variable was discarded from the model. Only covariates with a p-value <0.10 remained in the final model. These results were contrasted with backward stepwise selection in order to find potential changes in the results. The odds ratio and 95% confidence limit were calculated too. The area under the ROC curve (AUC) was measured to assess the goodness-of-fit. Finally, we checked collinearity among the different variables assessed according to the variation inflation factor (VIF).

TABLE 1 Socio-demographic and clinical characteristics of the sample according to malnutrition grade based on CONUT severity score.

	No malnutrition $n = 146$ **(57.5%)**	**Mild malnutrition** $n = 100$ **(39.4%)**	**Moderate or severe malnutrition** $n = 8$ **(3.1%)**	**Test; *p*-value** $n = 254$
Sex (% females)	46.6	40.0	25.0	$\chi^2 = 2.1$; $p = 0.351$
Age, mean (SD)	46.1 (15.8)	43.6 (17.1)	37.6 (14.8)	$F = 2.1$; $p = 0.351$
Days of hospitalization, median {IQR}	19.5 {13.8–25.3}	20.0 {13.3–27.0}	14.5 {8.5–23.5}	$F = 0.4$; $p = 0.681$
Urgent admission (%)	82.2	79.0	75.0	$\chi^2 = 0.8$; $p = 0.655$
Readmission (%)	6.2	7.0	12.5	$\chi^2 = 1.2$; $p = 0.541$
Treatment				
Benzodiazepines (%)	37.0	28.0	37.5	$\chi^2 = 2.3$; $p = 0.304$
Antidepressants (%)	39.7	29.0	50.0	$\chi^2 = 8.8$; $p = 0.224$
Mood stabilizers (%)	19.2	11.0	25.0	$\chi^2 = 5.2$; $p = 0.238$
Antipsychotics (%)	44.5	43.0	25.0	$\chi^2 = 3.5$; $p = 0.702$
Polypharmacy (≥3) (%)	22.6	17.0	12.5	$\chi^2 = 8.9$; $p = 0.624$
ECT (%)	8.2	7.0	0.0	$\chi^2 = 0.2$; $p = 0.900$
Medical conditions (%)	33.6	35.0	12.5	$\chi^2 = 1.5$; $p = 0.509$
Psychiatric disorders				
Bipolar disorder (%)	17.8	18.0	0.0	$\chi^2 = 1.2$; $p = 0.576$
Bipolar depression (%)	14.4	11.0	0.0	$\chi^2 = 1.1$; $p = 0.589$
Depressive disorder (%)	26.7	28.0	0.0	$\chi^2 = 2.8$; $p = 0.260$
Psychotic disorder (%)	52.7	46.0	62.5	$\chi^2 = 1.6$; $p = 0.482$
Schizophrenia (%)	21.9	17.0	25.0	$\chi^2 = 1.2$; $p = 0.601$
Schizoaffective disorder (%)	8.9	12.0	0.0	$\chi^2 = 0.9$; $p = 0.605$
Substance use disorder (%)	66.4	64.0	75.0	$\chi^2 = 0.4$; $p = 0.853$
AUD (%)	32.2	25.0	37.5	$\chi^2 = 1.9$; $p = 0.374$
Non-AUD (%)	58.2	57.0	50.0	$\chi^2 = 0.3$; $p = 0.864$
Organic mental disorder (%)	6.8	7.0	25.0	$\chi^2 = 3.4$; $p = 0.188$
Obesity (%)	26.0	13.8	16.7	$\chi^2 = 4.2$; $p = 0.106$
BMI, mean kg/m^2 (SD)	27.0 (6.6)	24.0 (5.2)	24.0 (4.4)	$F = 5.9$; $p < 0.01$**
Blood test parameters				
Cholesterol, mean mg/dL (SD)	191.6 (41.0)	144.7 (29.5)	128.5 (21.9)	$F = 54.9$; $p < 0.01$**
Triglycerides, mean mg/dL (SD)	123.8 (63.2)	91.2 (38.3)	78.5 (27.2)	$F = 12.0$; $p < 0.01$**
Albumin, mean g/L (SD)	41.4 (9.0)	39.7 (3.6)	31.3 (3.0)	$F = 8.3$; $p < 0.01$**
Total proteins, mean g/L (SD)	67.3 (5.2)	65.8 (7.4)	57.9 (6.9)	$F = 9.5$; $p < 0.01$**
Transferrin, mean g/L (SD)	2.6 (1.6)	2.4 (0.4)	2.0 (0.5)	$F = 1.7$; $p = 0.188$
Transferrin saturation, mean % (SD)	26.4 (11.6)	21.3 (12.4)	15.9 (8.0)	$F = 7.3$; $p < 0.01$**
Prealbumin, mean g/L (SD)	0.3 (0.1)	0.2 (0.1)	0.1 (0.1)	$F = 34.8$; $p < 0.01$**
Iron, mean μg/dL (SD)	90.6 (37.6)	69.4 (36.1)	46.1 (24.6)	$F = 13.2$; $p < 0.01$**
Lymphocytes, mean $n \times 10^9$/L (SD)	2.1 (0.5)	1.7 (0.8)	0.8 (0.4)	$F = 22.8$; $p < 0.01$**
Zinc, mean μg/dL (SD)	93.03 (16.1)	88.1 (13.7)	68.3 (20.3)	$F = 10.4$; $p < 0.01$**

Abbreviations: AUD, alcohol use disorder; BMI, body mass index; ECT, electroconvulsive therapy; IQR, interquartile range; SD, standard deviation.
**Significant at $p < 0.01$.

All statistical analyses were performed by the use of a confidence interval of 95%, and significance was set at $p < 0.05$. Analyses were conducted with SPSS version 25.0.

3 | RESULTS

3.1 | Characteristics of the sample by nutritional status

Among the 357 individuals admitted to the acute psychiatric ward who were recruited, 254 subjects were suitable for analysis. Socio-demographic and clinical characteristics of the whole sample are available in Table 1.

According to the CONUT scores, 57.5% showed a normal nutritional status (scores 0–1), 39.4% showed mild malnutrition (scores 2–4), and 3.1% moderate or severe malnutrition (scores >4). No significant differences were found in gender and mean age between groups. Treatments received during the hospitalization and frequency of each diagnosis did not reveal significant differences between groups.

3.2 | Main findings

3.2.1 | Length of stay

Grade of malnutrition calculated by CONUT score did not show a significant correlation with the length of stay. The only parameters that showed a significant inverse correlation with length of stay were plasmatic protein levels, transferrin saturation, and iron levels, being these differences significant at $p < 0.01$.

In the lineal regression analyses, only low total proteins, iron levels, and transferrin saturation showed an association with greater length of stay ($p < 0.01$ and $p < 0.05$, respectively), as represented in Table 2. However, the multiple regression analysis did not show a significant association with the length of stay ($R^2 = 0.03$, $p = 0.053$). No significant differences were found when length of stay was compared between patients with and without malnutrition according to the CONUT score (median 20.00 days, IQR {13.0–26.8}; median 19.50 days, IQR {13.8–25.3}, respectively).

No significant differences were found in terms of days of hospitalization according to the treatment with ECT, antidepressants, mood stabilizers, antipsychotics, benzodiazepines, nor in patients treated with 3 or more of these drug families at the same time. When length of stay was compared according to the presence of bipolar disorder, major depressive disorder, schizophrenia, schizoaffective disorder, substance use disorder, medical comorbidity or organic mental disorder, no differences were found between groups.

3.2.2 | Nutritional status

Negative correlations with the nutritional status assessed with the CONUT total score were found with BMI and

TABLE 2 Factors associated with length of stay.

	Unstandardized coefficient	95% CI		*p*-value	Standardized coefficient	R^2
		LL	UL			
Age (years)	0.027	−0.053	0.107	0.504	0.036	0.001
Cholesterol (mg/dL)	−0.010	−0.043	0.24	0.572	−0.032	0.001
Albumin (g/L)	−0.018	−0.236	0.201	0.873	−0.010	0.000
Lymphocytes ($n \times 10^9$/L)	−1.570	−3.456	0.317	0.103	−0.089	0.008
Triglycerides (mg/dL)	0.008	−0.015	0.030	0.505	0.037	0.001
Total proteins (g/L)	−0.204	−0.391	−0.017	0.03*	−0.119	0.014
Transferrin (g/L)	−0.244	−1.536	1.049	0.711	−0.023	0.001
Prealbumin (g/L)	−13.068	−35.668	9.533	0.256	−0.072	0.005
Transferrin saturation (%)	−0.152	−0.286	−0.018	0.026*	−0.140	0.020
Iron (μg/dL)	−0.057	−0.099	−0.015	0.008**	−0.167	0.028
Zinc (μg/dL)	−0.048	−0.153	0.058	0.376	−0.057	0.003
BMI (kg/m^2)	0.171	−0.077	0.420	0.175	0.082	0.007
CONUT score	0.918	−0.191	2.027	0.104	0.102	0.010

Note: Linear regression analyses were performed. Statistical significance was set at $p < 0.05$.
*Significant at $p < 0.05$.**Significant at $p < 0.01$.

all the analytical parameters, including total cholesterol, triglycerides, albumin, total proteins, prealbumin, iron, lymphocytes, zinc, and transferrin saturation, being all these negative correlations statistically significant ($p < 0.01$) except for transferrin, and also not observed with length of stay or age.

In addition, most of the blood parameters assessed showed to be correlated with other nutritional factors, as shown in Supplementary Table 1.

When blood parameters were compared between groups, median cholesterol levels in patients with malnutrition were 139.00 mg/dL (IQR {124.00–162.00}), whereas in those without malnutrition median levels were 185.00 mg/dL (IQR {165.00–206.00}; $p < 0.001$). Median zinc levels were 87.50 μg/dL (IQR {77.25–95.00}) in patients with malnutrition and 91.00 μg/dL (IQR {81.00–104.00}) in patients without malnutrition. These differences were significant at $p < 0.01$. In addition, median ranges of lymphocyte count were significantly different between groups, with 2.10×10^9/L (IQR {1.70–2.50}) in the group without malnutrition and 1.40×10^9/L (IQR {1.10–2.00}) in the malnutrition group ($p < 0.001$). Median differences between groups in BMI were also observed, with 26.10 kg/m^2 (IQR {22.35–29.79}) in the group without malnutrition and 22.74 kg/m^2 (IQR {20.00–27.17}) in the other group ($p < 0.001$). In addition, patients with malnutrition showed lower median albumin levels compared with patients without malnutrition (39.00 g/L, IQR {36.25–42.00}, vs. 41.00 g/L, IQR {38.00–43.00} respectively; $p < 0.05$). Notwithstanding, they also presented significantly lower median levels of triglycerides (81.50 mg/dL, IQR {63.00–109.00}, vs. 107.00 mg/dL, IQR {84.00–141.00}; $p < 0.001$), total proteins (65.00 g/L, IQR {61.00–69.00}, vs. 67.00 g/L, IQR {64.00–70.00}; $p < 0.05$), prealbumin (0.20 g/L, IQR {0.16–0.24}, vs. 0.25 g/L, IQR {0.21–0.30}; $p < 0.001$), and transferrin saturation (19.10%, IQR {11.85–25.95}, vs. 25.05%, IQR {17.58–32.45}, $p < 0.001$), and lower mean iron levels (67.65 μg/dL, SD 35.81, vs. 90.62 μg/dL, SD 37.60; $p < 0.001$), not showing differences in median transferrin levels (2.30 g/L, IQR {2.10–2.60}, vs. 2.40 g/L, IQR {2.20–2.75}; $p = 0.11$). These results are represented in Table 3.

In the assessment of potential variables associated with malnutrition, univariate analyses through binary logistic regression showed a significant association for cholesterol levels, triglycerides, albumin, total proteins, transferrin, prealbumin, transferrin saturation, iron, lymphocytes, zinc, and BMI. However, in the multivariate analysis, only cholesterol levels, lymphocyte count, zinc levels and BMI showed significant differences according to nutritional status (Figure 1). These results did not vary when backward and forward stepwise selection algorithms were used. The AUC value was obtained to assess the goodness-of-fit, which resulted 0.955 (95% CI 0.92–0.99). No evidence of collinearity was observed among cholesterol levels, lymphocyte count, zinc levels, and BMI, since the VIF resulted lower than 5 for all of them. Univariate and multivariate logistic regression is shown in Table 4.

Regarding pharmacological treatment, no significant differences were observed in the proportion of individuals treated with ECT, antidepressants, mood stabilizers, antipsychotics, benzodiazepines, nor in patients treated with 3 or more of these drug families at the same time, when patients with and without malnutrition were compared.

TABLE 3 Differences in blood parameters between patients according to their nutritional status.

	No malnutrition	Malnutrition	*p*-value
Cholesterol (mg/dL), median {IQR}	185.00 {165.00–206.00}	139.00 {124.00–162.00}	<0.01**
Zinc (μg/dL), median {IQR}	91.00 {81.00–104.00}	87.50 {77.25–95.00}	<0.01**
Iron (μg/dL), mean (SD)	90.62 (37.60)	67.65 (35.81)	<0.01**
Lymphocytes ($n \times 10^9$), median {IQR}	2.10 {1.70–2.50}	1.40 {1.10–2.00}	<0.01**
BMI (kg/m^2), median {IQR}	26.10 {22.35–29.79}	22.74 {20.00–27.17}	<0.01**
Albumin (g/L), median {IQR}	41.00 {38.00–43.00}	39.00 {36.25–42.00}	<0.01**
Triglycerides (mg/dL), median {IQR}	107.00 {84.00–141.00}	81.50 {63.00–109.00}	<0.01**
Total proteins (g/L), median {IQR}	67.00 {64.00–70.00}	65.00 {61.00–69.00}	<0.01**
Prealbumin (g/L), median {IQR}	0.25 {0.21–0.30}	0.20 {0.16–0.24}	<0.01**
Transferrin saturation (%), median {IQR}	25.05 {17.58–32.45}	19.10 {11.85–25.95}	<0.01**
Transferrin (g/L), median {IQR}	2.40 {2.20–2.75}	2.30 {2.10–2.60}	0.11

Note: Mean, standard deviation, median and *p*-value are represented. Statistical significance was set at $p < 0.05$.
Abbreviation: BMI, body mass index.
**Significant at $p < 0.01$.

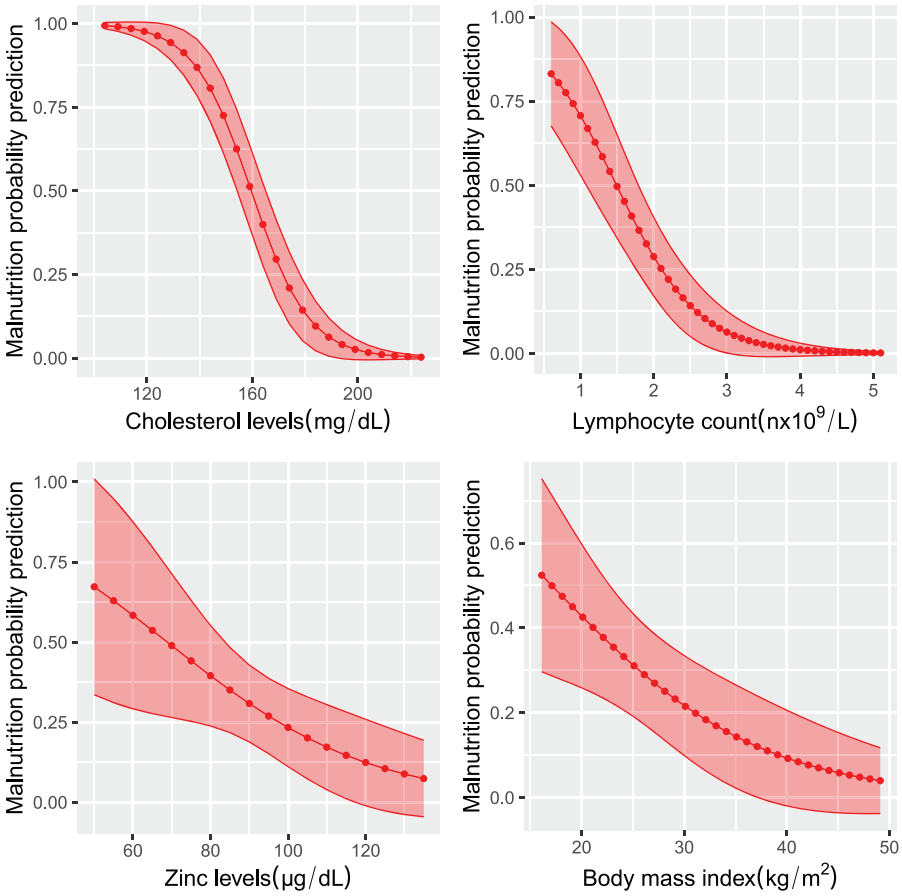

FIGURE 1 Malnutrition probability prediction by cholesterol levels, lymphocyte count, zinc levels, and body mass index according to a multivariate analysis.

TABLE 4 Factors associated with malnutrition.

	Univariate analysis				Multivariate analysis			
		95% CI				95% CI		
	OR	LL	UL	Sig (*p*-value)	OR	LL	UL	Sig (*p*-value)
Length of stay (days)	1.008	0.990	1.028	0.384				
Cholesterol (mg/dL)	0.946	0.933	0.960	<0.001**	0.913	0.888	0.938	<0.001**
Triglycerides (mg/dL)	0.984	0.977	0.991	<0.001**				
Albumin (g/L)	0.879	0.817	0.946	0.001**				
Total proteins (g/L)	0.948	0.909	0.988	0.012*				
Transferrin (g/L)	0.522	0.290	0.938	0.030*				
Prealbumin (g/L)	0.000	0.000	0.000	<0.001**				
Transferrin sat. (%)	0.959	0.936	0.982	0.001**				
Iron (µg/dL)	0.982	0.974	0.990	<0.001**				
Lymphocytes ($n \times 10^9$/L)	0.332	0.213	0.518	<0.001**	0.169	0.078	0.365	<0.001**
Zinc (µg/dL)	0.974	0.957	0.991	0.003**	0.964	0.930	1.000	0.048*
BMI (kg/m^2)	0.914	0.866	0.965	0.001**	0.903	0.832	0.980	0.014*

Note: Binary logistic regression was performed. Statistical significance was set at $p < 0.05$.
Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; LL, lower level; OR, odds ratio; UL, upper level.
**Significant at $p < 0.01$.*Significant at $p < 0.05$.

In addition, no significant differences were found in the proportion of patients with bipolar disorder, major depressive disorder, schizophrenia, schizoaffective disorder, substance use disorder, medical comorbidity or organic mental disorder between the two groups.

3.2.3 | Body mass index

Patients were grouped into weight categories using BMI classification as defined by the World Health Organization (WHO) (underweight, BMI < 18.50; normal weight, BMI 18.50–24.99; overweight, BMI 25.00–29.99; and obese, BMI ≥ 30.00).[22]

Considering the whole sample, the percentage of underweight patients was 6.1%, normal weight 47.5%, overweight 26.3%, and obese 20.1%.

In the subsample of well-nourished patients according to the CONUT score, the percentage of underweight people was 5.5%, normal weight 40.9%, overweight 29.1%, and obesity 24.5%. Among patients with a poorer nutritional status, the frequency of underweight was 5.7%, normal weight 58.6%, overweight 21.8%, and obesity 13.8%. Differences between groups did not reach statistical significance.

4 | DISCUSSION

It is widely known that several psychiatric disorders and pharmacological treatments commonly used in psychiatric clinical practice have an impact on metabolism and medical comorbidities.[23] Moreover, the available evidence indicates that somatic conditions, such as impaired glucose metabolism, may have an impact on the course of the psychiatric illness.[21] However, scarce data are available regarding nutritional status in acute psychiatric patients, being most of the evidence related to patients with eating disorders.[9,24,25]

The present investigation shows through a cross-sectional study a considerable rate of malnutrition (defined by CONUT score ≥ 2) in a sample of patients admitted in an acute psychiatric unit (42.5%), which is consistent with other studies using the same nutritional assessment tool.[26,27] Considering the correlation of CONUT scores with a worse clinical prognosis in somatic disorders, including longer hospitalizations,[4,28] this study aimed to evaluate the association of malnutrition with the length of stay and also to find nutritional parameters that might better predict the nutritional status of patients.

The analyses performed did not reveal a significant association between malnutrition and length of stay when nutritional status was assessed with the CONUT score. However, plasmatic protein levels, transferrin saturation and iron levels showed a significant inverse correlation with the days of hospitalization, indicating a potential effect of nutritional status on the course of acute psychiatric admissions. Additionally, low iron levels showed an association with greater length of stay. These results suggest that, although specific nutritional parameters have shown to be related to greater length of stay, the CONUT score might not be the best short-term predictor in psychiatric hospitalizations. This could be associated with the fact that, in the context of an acute psychiatric ward, behavioral abnormalities and psychopathology are treated in an individualized manner, with some patients with severe episodes being treated with higher doses of the indicated treatment or with different drugs. Thus, the length of stay might not be reflecting the severity of the acute episodes in all cases. Based on these findings, further studies using prospective models should evaluate if this score is associated with different course of the psychiatric illnesses in the long term, and if the nutritional parameters associated with a poorer short-term prognosis should be considered risk factors also for an adverse course of illness.

In this study, the correlation of specific nutritional parameters with nutritional status found that, apart from those included in the CONUT screening tool, low zinc, iron, total proteins, prealbumin, transferrin, triglyceride levels, a low transferrin saturation index, and BMI, were indicators of a poorer nutritional status. Most parameters showed a correlation between them. Results indicating that lower BMI, contrary to the expected, is associated with a poorer nutritional status might suggest that this subgroup of patients might present reduced food intake or higher tendency to a poorer self-care, but further evidence should be conducted in order to confirm this hypothesis. However, as also seen in our results, it is not uncommon to find a significant proportion of patients with overweight, which can be due to several factors, such as lifestyle and habits, pharmacological treatments and mental illnesses by themselves.

Our results demonstrate a strong relation of several analytical parameters assessed with the nutritional status and allow the identification of specific subgroups, such as those with greater alteration of nutritional parameters, that may present longer courses of disease, having also demonstrated in previous evidence worse medical prognosis.[4]

Even though there was an important correlation between different nutritional parameters and all of them

were correlated with malnutrition, this study identified cholesterol levels, lymphocyte count, zinc levels, and BMI as independent factors associated with malnutrition, which highlights the importance of their assessment in clinical practice.

Psychiatric diagnoses or treatment received did not seem to have influence over nutritional status or days of hospitalization. Thus, this study does not identify specific psychiatric diagnoses or psychotropic drugs that might increase the risk for malnutrition or for a worse course of acute psychiatric admissions, basing the associated findings on analytical parameters.

In 13.8% of the patients, obesity with nutritional deficiency according to CONUT score was found, which emphasizes the importance to characterize the different nutritional profiles of these patients according to their nutritional status.[29,30] This might allow clinicians to develop adequate nutritional risk screening tools considering specificity of this population[10,11,31] and determined approaches for different clinical situations.[32,33]

According to our findings, clinicians should include nutritional status-related analytical parameters for a global assessment of the nutritional status, and to consider them as factors that might influence the organic and mental well-being of patients. The authors recommend a periodical study of patients' nutritional status from the outpatient unit and not only when they are hospitalized, since this might allow the identification of determined subgroups that could benefit from psychosocial and lifestyle interventions, the prescription of nutritional supplementation in specific cases,[32] as well as the implementation of individual or group sessions aimed to the assessment of daily habits and to the promotion of healthy routines. These strategies might provide patients some skills that lead to an improvement of their nutritional status, their medical and psychiatric prognosis and their quality of life. Specifically, physicians should pay attention to those patients with poor social support and severe mental illnesses in order to detect and manage a potential malnutrition status.

The admission in an acute psychiatric ward should serve as an opportunity for clinicians to identify existing abnormalities, since a poor nutritional status has been correlated with higher adverse prognostic factors.[4,28] As found in this work, altered levels of cholesterol, lymphocyte count, zinc, and low BMI should be considered as potential indicators of a poor nutritional status. Patients in which different nutritional parameters were found at insufficient levels might be a target for nutritional and lifestyle interventions aimed to improve their physical and mental health.

The results obtained from this study aim to drive a line of research in which nutritional and metabolic data may serve clinicians for wider interventions beyond the improvement of the psychiatric episodes and medical comorbidities. Since periodical blood tests and anthropometric measures are performed in outpatient units, the design of new studies targeting nutritional and metabolic parameters in psychiatric patients might be also useful in order to distinguish in the future profile of patients who are at higher risk for either suffering medical comorbidities or presenting with adverse circumstances related to their psychiatric disorder. Further studies will also elucidate the influence of pharmacological treatment and specific psychiatric disorders in patients' nutritional status. In addition, future evidence will allow to study the relationship of poorer nutritional status and prognostic factors related to the psychiatric illness, such as suicidal behavior, frequency of episodes or number of admissions.

Our study comes with some strengths and limitations. To the authors' knowledge, there is a lack of evidence about the global nutritional status of psychiatric inpatients, with the exception of patients with eating disorders. The description of the nutritional status in psychiatric population might help determine the influence of pharmacological treatments, lifestyle habits, diet, and the different psychiatric illnesses on somatic health, and might allow the implementation of preventive or therapeutic interventions in specific profiles. The use of an objective tool to determine the nutritional status confers higher reliability to the results obtained. Regarding the limitations of this study, its cross-sectional design cannot reveal causal dynamics between considered variables, and cannot allow the inclusion of other nutritional factors. However, this cross-sectional study can represent a picture of the nutritional status of patients admitted in a psychiatric ward and is a first approach to study the interaction between specific factors related with their disease and malnutrition, which may in the future open new opportunities for individualized interventions. Studies in the recent future with larger samples and longitudinal data would be useful in order to progress in this field.

To conclude, our results showed that plasmatic protein levels, transferrin saturation and iron levels were inversely correlated with length of stay in patients admitted to an acute psychiatric ward, having low iron levels an association with greater length of stay. They suggest that nutritional status might influence the course of psychiatric admissions.

In acute psychiatric hospitalizations, the nutritional assessment should include the study of different parameters, such as cholesterol, albumin, lymphocyte count, zinc, iron, prealbumin, transferrin, triglycerides,

transferrin saturation, and BMI, which might allow the identification of patients with a poor nutritional status in which lifestyle interventions might be promoted with a special focus.

Future studies will allow to elucidate the relationship between nutritional status and other specific psychiatric prognostic factors apart from length of stay, such as suicidal behaviors, frequency of episodes or number of admissions.

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CONFLICT OF INTEREST STATEMENT

AGP has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag, Casen Recordati, LCN, Rovi and Lundbeck, outside the present work. MTPC has received financial support for CME activities and travel funds from Lundbeck, Pfizer, and Esteve. She reports no financial or other relationship relevant to the subject of this article. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. The rest of authors do not report any conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13598.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Reduced mitochondrial respiratory capacity in patients with acute episodes of bipolar disorder: Could bipolar disorder be a state-dependent mitochondrial disease?

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Abstract

Background: Bipolar disorder (BD) is a chronic and recurrent disease characterized by acute mood episodes and periods of euthymia. The available literature postulates that a biphasic dysregulation of mitochondrial bioenergetics might underpin the neurobiology of BD. However, most studies focused on inter-subject differences rather than intra-subject variations between different mood states. To test this hypothesis, in this preliminary proof-of-concept study, we measured in vivo mitochondrial respiration in patients with BD during a mood episode and investigated differences compared to healthy controls (HC) and to the same patients upon clinical remission.

Methods: This longitudinal study recruited 20 patients with BD admitted to our acute psychiatric ward with a manic ($n = 15$) or depressive ($n = 5$) episode,

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and 10 matched HC. We assessed manic and depressive symptoms using standardized psychometric scales. Different mitochondrial oxygen consumption rates (OCRs: Routine, Leak, electron transport chain [ETC], Rox) were assessed during the acute episode (T0) and after clinical remission (T1) using high-resolution respirometry at 37°C by polarographic oxygen sensors in a two-chamber Oxygraph-2k system in one million of peripheral blood mononuclear cells (PMBC). Specific OCRs were expressed as mean ± SD in picomoles of oxygen per million cells. Significant results were adjusted for age, sex, and body mass index.

Results: The longitudinal analysis showed a significant increase in the maximal oxygen consumption capacity (ETC) in clinical remission (25.7 ± 16.7) compared to the acute episodes (19.1 ± 11.8, $p = 0.025$), and was observed separately for patients admitted with a manic episode (29.2 ± 18.9 in T1, 22.3 ± 11.9 in T0, $p = 0.076$), and at a trend-level for patients admitted with a depressive episode (15.4 ± 3.9 in T1 compared to 9.4 ± 3.2 in T0, $p = 0.107$). Compared to HC, significant differences were observed in ETC in patients with a bipolar mood episode ($H = 11.7$; $p = 0.003$). Individuals with bipolar depression showed lower ETC than those with a manic episode ($t = -3.7$, $p = 0.001$). Also, significant differences were observed in ETC rates between HC and bipolar depression ($Z = 1.000$, $p = 0.005$).

Conclusions: Bioenergetic and mitochondrial dysregulation could be present in both manic and depressive phases in BD and, importantly, they may restore after clinical remission. These preliminary results suggest that mitochondrial respiratory capacity could be a biomarker of illness activity and clinical response in BD. Further studies with larger samples and similar approaches are needed to confirm these results and identify potential biomarkers in different phases of the disease.

KEYWORDS

biomarker, bipolar disorder, depression, mania, mitochondrial dysfunction

1 | INTRODUCTION

Bipolar disorder (BD) is a chronic and recurrent disease characterized by depressive and manic or hypomanic mood episodes.[1,2] Despite a proper treatment, patients with BD can suffer long-term consequences, such as reduced functionality, impaired quality of life and cognition, and medical comorbidities.[2,3]

Different studies have been published pointing to the role of mitochondrial function as a key element in the pathogenesis and pathophysiology of BD.[4–8] In fact, Morris, Berk and colleagues proposed in 2017 a model in which BD could be conceptualized as a biphasic disorder of energy availability, which would be increased in mania and decreased in depression.[4] The central hypothesis of this model is that the biphasic symptoms of BD, such as increased energy in mania and fatigue and psychomotor slowing in depression, could be associated with a biphasic dysregulation of mitochondrial bioenergetics. Mitochondrial dysfunction might serve as a state-dependent marker of the disorder, with increased mitochondrial function being characteristic of bipolar mania while decreased mitochondrial function being characteristic of bipolar depression.

In BD, decreases in mitochondrial respiration, high-energy phosphates and pH, changes in mitochondrial morphology and in mitochondrial DNA copy number,[9,10] mitochondrial DNA polymorphisms, as well as downregulation of nuclear mRNA molecules and proteins involved in mitochondrial respiration have been described.[11] In addition, increases in lactate levels have been identified in BD, which supports an altered mitochondrial oxidative phosphorylation that shifts the cellular bioenergetic system to anaerobic respiration.[12]

Indeed, increased lactate in major psychiatric disorders is one of the oldest biomarkers of all psychiatric disorders, first documented in 1934.[13]

The presence of mutations in mitochondrial DNA encoding mitochondrial complex subunits involved in electron transport chain (ETC) has been described in BD, as well as an increased complex I activity, decreased complex II and IV activities,[14,15] and changes at the mRNA and protein levels. Results from microarray and real-time quantitative polymerase chain reaction data revealed decreased expression in BD patients of many mRNAs coding for subunits of ETC complexes I–V.[14]

There are also many potential indirect mediators of mitochondrial function, such as oxidative stress and proinflammatory cytokines, that have been found increased in this disorder.[4,16,17] Indeed, inflammation and oxidative stress are likely upstream drivers of impaired mitochondrial biogenesis—for a review please see Reference 18.

Finally, different studies have correlated BD with metabolic disorders such as an increased body mass index (BMI) and insulin resistance,[19] and have postulated that disruptions in the molecular and cellular network regulating energy expenditure and mitochondria-mediated functions could be associated with "BD-related phenomena" and the longitudinal progression typically associated with both the primary psychiatric disorder, neuroprogression, and somatic comorbidity, somatoprogression.[19–21]

Despite changes in activity and energy availability observed in different stages of this disease, so far, the assessment of mood episodes and treatment response is based on clinical interviews and on the use of validated questionnaires,[22] and no biomarkers have been implemented in clinical practice to support diagnostic and therapeutic processes.[23,24]

Even though mitochondrial changes have been described in BD at different levels, the available studies often compare this population with healthy controls (HCs). Nevertheless, little evidence is available assessing intra-individual differences in mitochondrial function between different states of the illness, which is needed given the state dependent inter-individual variability in mitochondrial function. Over the last decade, different studies have reported ETC dysfunction in BD. However, in vivo cellular mitochondrial respiration has been assessed in subjects with major depressive disorders[25] and BD[26,27] and compared it with mitochondrial respiration in HC, but has not been studied in different phases of BD. In addition, these studies have been conducted with small samples.

Thus, considering the high variability in mitochondrial function between different individuals and the diverse clinical situations that patients with BD might present, there is a need of evidence focusing on the identification of intra-individual differences in different stages of the disease. The hypothesis of this study was that there is a potential variation in mitochondrial respiration in acute states of the disease, with an increase in mitochondrial respiration in mania and a decrease in depression compared to euthymic states and HC. The exploration of in vivo mitochondrial respiration might support previous findings regarding mitochondrial function in BD and also allow to identify potential differences in mitochondrial function between patients and HC. Therefore, in this study, to deepen into disease physiopathology and eventual biomarker or therapeutic target identification, we explored differences: (1) intra-individually: longitudinally within patients during an acute mood episode of BD and after clinical remission, and (2) inter-individually: between patients with BD on acute mood episodes and HC.

Significant outcomes

- Acute episodes of bipolar disorder were associated with reduced maximum mitochondrial respiratory capacity compared to euthymic states in the same individuals.
- Maximum mitochondrial respiration was significantly different between manic and depressive patients during the acute episode and healthy controls.
- Patients with manic episodes showed higher mitochondrial oxygen consumption capacity than subjects under a depressive episode.

Limitations

- The sample obtained in the study was limited and did not include patients with mixed episodes or with a long course of illness.
- Only patients with severe acute mood episodes of bipolar disorder requiring acute hospitalization were included.
- The results obtained by mitochondrial respiration analyses were not contrasted with other methods aimed to assess mitochondrial function.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The current work is part of a financed longitudinal study (PI21/00169) aimed to assess intra-individual

differences in bioenergetics and mitochondrial function in patients with BD admitted to our acute psychiatric ward during an acute episode (T0) and after clinical remission (T1).

In the current study, we examined in vivo mitochondrial respiratory capacity in living cells of patients with BD type I on acute manic and depressive episodes, according to DSM-5 criteria,[28] admitted to our acute psychiatric unit. Patients were assessed at two times, during the acute episode (T0) and after symptomatic remission (T1), defined as standardized clinical scores ≤7 at YMRS or HDRS (i.e., symptoms absent or nearly absent),[29] before hospital discharge. A course of disease shorter than 10 years was necessary for patient recruitment. Patients or HC with intellectual quotient lower than 80, with substance use disorders other than cannabis, and with any cardiac, auto-immune, inflammatory illness or with an acute infectious illness were excluded from this study, as well as those with known history of familial mitochondrial disease. In the control group, only participants with no family history of BD or personal psychiatric history were recruited. All patients were recruited by assistant and researcher psychiatrists (IP and AGP) after their admission in our acute unit. Matched HC were recruited by the same staff.

The capacity to provide informed consent was assessed before entering the study and re-assessed after remission. We also recruited HC, based on the same exclusion criteria. This study was approved by the Hospital Clínic Research Ethics Committee (protocol code: HCB/2021/0358).

2.2 | Sociodemographic and clinical variables

Relevant sociodemographic and clinical variables (i.e., current and previous diagnosis, years of illness, psychiatric and medical comorbidities) were obtained. During the initial interview, manic and depressive symptoms were assessed respectively using standardized psychometric scales: the Young Mania Rating Scale (YMRS)[30,31] and the 17-item Hamilton Depression Rating Scale (HDRS).[32,33] In addition, Functioning Assessment Short Test (FAST),[34] Clinical Global Impression Scale – Severity (CGI-S),[35] International Physical Activity Questionnaire (IPAQ)[36] and a 17-score scale aimed to measure adherence to Mediterranean Diet (PREDIMED-17)[37] were administered. Lastly, Fagerström[38] and Alcohol Use Disorders Identification Test (AUDIT)[39] scales scores were also obtained at T0. After clinical remission (T1), HDRS, YMRS, FAST, IPAQ, CGI-S and CGI-Improvement (CGI-I) scales were administered. Clinical variables were assessed at T0 and T1.

2.3 | Sample processing and mitochondrial respiration

In patients, different mitochondrial oxygen consumption rates (OCRs) were assessed at T0 and T1, right after the extraction of peripheral blood mononuclear cells (PBMCs) obtained by a Ficoll density gradient centrifugation procedure. In HC, this procedure was conducted once. To determine PBMCs' OCRs at T0 and T1, a million of living cells resuspended in PBS1x were used. Patients and HC were fasted at the time of the blood extraction, which was conducted at 8.30–9 a.m. and was consistent in all participants. Sample processing was conducted right after the sample extraction and took around two and a half hours to isolate PBMCs, which were then used to assess mitochondrial respiration. High-resolution respirometry was immediately performed in fresh cells at 37°C by polarographic oxygen sensors in a two-chamber Oxygraph-2k system according to manufacturer's instructions (OROBOROS Instruments, Innsbruck, Austria). Specific OCRs were obtained (Routine: basal oxygen consumption with no exogenous substrates; Leak: oxygen consumption not coupled to ATP synthesis; ETC: maximal capacity of the ETC; and Rox: oxygen consumption not linked to PBMCs' mitochondrial activity). Routine, Leak and ETC OCRs were registered by subtracting the rates from Rox as it is considered unspecific and non-mitochondrial oxygen consumption. Manual injection of inhibitors and uncouplers was performed using Hamilton syringes (Hamilton Company, Reno, NV, USA). Thus, measurement of OCR was done at baseline (Routine) and after sequential injections of: (1) oligomycin (1.5 mM), an ATP synthase inhibitor, (2) carbonyl cyanide 3-chlorophenylhydrazone (CCCP) (1 mM), a mitochondrial uncoupler, and (3–4) rotenone (2 mM) and antimycin A (0.2 mM), which are complex I and complex III inhibitors, respectively.

Oxygen uptake was calculated per million cells. Results are expressed as picomoles of oxygen per million cells (pmol O_2/million).

2.4 | Statistical analysis

Statistical analyses were computed with "IBM SPSS Statistics 25" (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.), GraphPad Prism and R Statistics. The normality of clinical and experimental parameters was assessed using the Kolmogorov–Smirnov test. Results from quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile

range (IQR). Results from categorical variables were shown as frequencies (number and percentage).

T-test, Mann Whitney U and Kruskal Wallis tests were used for mean comparisons between groups, using *T*-tests for data that were normally distributed. Chi-square tests were used for the comparison of categorical variables, and Fisher exact tests were performed when the expected cells were lower than five. For intra-subjects' comparisons, paired *T*-tests and Wilcoxon matched-pairs signed rank tests were used. Subsequently, significant results were controlled for age, sex and BMI with an ANCOVA analysis. A linear mixed regression was performed with the turkey method for multiple comparisons in order to report intra- and inter-individual variability and also the effect of time, group and time and group, controlled for the smoking status. All statistical analyses were performed by the use of a confidence interval of 95%, and statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Characteristics of the sample

A total of 20 subjects with BD during acute mood episodes (15 manic, 5 depressed) admitted to an acute psychiatric ward were recruited and included in the analysis at admission (T0) and after symptomatic remission (T1). Sociodemographic and clinical characteristics of patients are detailed in Table 1. In addition, mitochondrial respiration was assessed in 10 HC. Scales scores of patients with BD at baseline (T0) and after remission (T1) are detailed in Table 2.

Among HC, the mean age was 29.5 ± 3.5 and there were 50% females, which did not differ significantly from the patients' cohort.

Compared to patients admitted with a manic episode, patients with a depressive episode had a higher mean age than those with a manic episode (37.2 vs. 27.0 years; $t = -2.3$, $p = 0.034$), higher duration of affective illness ($Z = -3.3$, $p < 0.01$), and higher number of previous depressive episodes ($Z = -3.6$, $p < 0.001$). Accordingly, depressive patients were more likely to be already attending a psychiatric outpatient unit at the time of their admission (100% vs. 26.7%; $F = 8.1$, $p < 0.01$) and were less likely to have psychotic symptoms (20% vs. 93.3%; $F = 10.8$, $p < 0.01$). Only six manic patients discontinued pharmacological treatment before hospitalization (40%), but none from the depressive group.

The mean YMRS score for patients with manic episodes was 24.6 ± 9.9 at T0, with a reduction to 3.7 ± 2.7 at T1 ($Z = -3.4$, $p = 0.001$). The mean HDRS score for patients with bipolar depression was 18.0 ± 9.4 at T0, with a reduction to 5.2 ± 2.0 at T1 ($Z = -1.8$, $p = 0.068$). After clinical remission (T1), median FAST total score was higher in bipolar depression ($Z = 6.5$, $p < 0.01$), and median IPAQ total score was higher in mania ($Z = 2.3$, $p < 0.05$).

3.2 | Intra-individual comparisons in mitochondrial respiration between acute episodes of BD and euthymia

Except for ETC, the specific oxygen uptake rates (Routine, Leak, Rox) did not follow a normal distribution.

Intra-subject longitudinal comparisons between acute mood episodes (T0) and clinical remission (T1) for the overall patients' sample are shown in Figure 1. A significant increase in the maximal oxygen consumption capacity (ETC) was observed in T1 (25.7 ± 16.7) compared to T0 (19.1 ± 11.8, $p = 0.025$). Routine and Leak OCRs did not show significant changes between both phases, despite they reproduced similar trends than ETC state (higher in T1).

Specific differences between T0 and T1 for manic and depressive patients are represented in Figure 2. Manic patients showed a tendency to increase their maximal respiratory capacity (ETC) after clinical remission (22.3 ± 11.9 vs. 29.2 ± 18.9, $p = 0.076$).

Patients admitted with a depressive episode also showed higher ETC means in T1 (15.4 ± 3.9) compared to T0 (9.4 ± 3.2), with non-significant differences ($p = 0.107$). Results from the pairwise analysis for multiple comparisons reporting estimated intra-individual mean differences between T0 and T1 among the overall patients' sample, manic and depressive groups are represented in Table 3.

3.3 | Inter-individual comparisons in mitochondrial respiration between HC and acute episodes of BD

Inter-subject comparisons of mitochondrial respiration are shown in Figure 3. When HC were compared with the overall patients at admission, no significant differences were found in Routine (5.91 ± 1.34 vs. 8.49 ± 8.28 respectively; $Z = -0.09$, $p = 0.948$), Leak (1.06 ± 0.47 vs. 0.84 ± 1.82 respectively; $Z = -0.13$, $p = 0.914$) or ETC (16.36 ± 3.68 vs. 19.09 ± 11.84 respectively; $t = -0.94$, $p = 0.355$). However, when HC, manic and depressive patients at T0 were compared, significant differences were observed in ETC ($H = 11.7$; $p = 0.003$). Age, sex, and BMI did not influence the previous results.

TABLE 1 Socio-demographic and clinical characteristics of the sample.

	Mania	Depression	Healthy controls	Test; *p*-value
	***n* = 15 (50%)**	***n* = 5 (16.7%)**	***n* = 10 (33.3%)**	***n* = 30**
Sex, *n* females (%)	9 (60.0)	3 (60.0)	5 (50.0)	$F = 0.3$; $p = 0.873$
Age, mean (SD)	27.0 (6.9)	37.2 (13.0)	29.5 (3.5)	$F = 3.6$; $p = 0.041$*
BMI (T0), mean (SD)	22.4 (3.2)	23.9 (2.4)	22.4 (1.7)	$F = 0.7$; $p = 0.520$
Abdominal circumference (T0), mean cm (SD)	82.5 (9.5)	88.0 (9.2)	80.0 (10.1)	$F = 1.2$; $p = 0.332$
Number of total previous episodes, mean (SD)	1.3 (1.3)	5.0 (3.5)	0.0 (0.0)	$F = 26.4$; $p = 0.000$**
Months from onset of first affective episode, median (IQR)	16.0 (0.0–72.0)	148.0 (132.0–246.0)	—	U = −3.3; $p = 0.001$**
Age of onset of BD, median (IQR)	24.0 (21.0–30.0)	21.0 (19.0–40.0)	—	U = 0.0; $p = 0.965$
Age at first hospitalization, median (IQR)	22.0 (20.0–30.0)	21.0 (16.5–40.0)	—	U = −0.4; $p = 0.661$
Number of previous psychiatric hospitalizations, median (IQR)	1.0 (0.0–2.0)	1.0 (0.5–4.0)	—	U = −1.2; $p = 0.216$
Number of previous manic episodes, median (IQR)	0.0 (0.0–1.0)	1.0 (0.0–3.5)	—	U = −1.2; $p = 0.216$
Number of previous depressive episodes, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–3.0)	—	U = −3.6; $p = 0.000$**
Previous psychiatric diagnosis, *n* (%)	11 (73.3)	5 (100)	0 (0)	$F = 18.2$; $p = 0.000$**
Current psychiatric follow-up, *n* (%)	4 (26.7)	5 (100)	0 (0)	$F = 16.0$; $p = 0.000$**
Life stressor, *n* (%)	5 (33.3)	3 (60.0)	0 (0)	$F = 6.8$; $p = 0.033$*
Psychotic symptoms, *n* (%)	14 (93.3)	1 (20.0)	—	$F = 10.8$; $p = 0.005$**
Delusions, *n* (%)	13 (86.7)	1 (20.0)	—	$F = 7.9$; $p = 0.014$*
Hallucinations, *n* (%)	6 (40.0)	0 (0.0)	—	$F = 2.9$; $p = 0.260$
Cannabis use, *n* (%)	6 (40.0)	0 (0.0)	0 (0.0)	$F = 7.5$; $p = 0.024$
Somatic illness, *n* (%)	2 (13.3)	1 (20.0)	2 (20.0)	$F = 0.2$; $p = 0.887$
Family psychiatric history, *n* (%)	9 (60.0)	4 (80.0)	2 (20.0)	$F = 6.0$; $p = 0.050$
Family history of BD, *n* (%)	5 (33.3)	2 (40.0)	0 (0.0)	$F = 4.7$; $p = 0.097$
Treatment discontinuation, n (%)	6 (40.0)	0 (0.0)	—	$F = 5.8$; $p = 0.031$*
Living alone, *n* (%)	1 (6.7)	1 (20.0)	1 (10.0)	$F = 0.7$; $p = 0.690$
Working activity, *n* (%)	6 (40.0)	3 (60.0)	10 (100)	$F = 9.3$; $p = 0.009$**
Pharmacological treatment				
Lithium, *n* (%)	13 (86.7)	4 (80.0)	—	$F = 0.1$; $p = 0.601$
Anticonvulsants, *n* (%)	1 (6.7%)	3 (60.0)	—	$F = 6.7$; $p = 0.032$
Second-generation AP, *n* (%)	15 (100)	5 (100)	—	—
Antidepressants, *n* (%)	0 (0.0)	0 (0.0)	—	—
Benzodiazepines, *n* (%)	8 (53.3)	5 (100)	—	$F = 3.6$; $p = 0.083$

Abbreviations: AP, antipsychotics; BD, bipolar disorder; BMI, body mass index; IQR, interquartile range; SD, standard deviation.
*$p < 0.05$.**$p < 0.01$.

When manic and depressive patients were compared between them at T0, those with bipolar depression showed lower ETC rates (9.4 ± 3.2) than those with a manic episode (22.3 ± 11.9; $t = -3.7$; $p = 0.001$) (Figure 4). No significant differences were observed in Routine or Leak between mania and bipolar depression. Again, age, sex and BMI did not influence the previous results. Main effects of group, time and interaction of group and time corrected for the smoking status are represented in Table 4.

TABLE 2 Scales scores of the sample at baseline (T0) and endpoint (T1).

	Manic, $n = 15$ (75%)		Depressive, $n = 5$ (25%)		Test; p-value, $n = 20$	
	T0	T1	T0	T1	T0	T1
HDRS total score, mean (SD)	2.7 (2.3)	2.3 (2.6)	18.0 (9.4)	5.2 (2.0)	$t = 3.6$; $p = 0.022$*	$t = 2.3$; $p = 0.034$*
YMRS total score, mean (SD)	24.6 (9.9)	3.7 (2.7)	2.6 (4.3)	0.4 (0.9)	$t = -4.8$; $p = 0.000$**	$t = -4.1$; $p = 0.001$**
FAST total score, median (IQR)	17.0 (2.0–40.0)	3.0 (0.0–14.0)	40.0 (22.0–56.0)	33.0 (16.5–45.5)	$Z = -1.6$; $p = 0.116$	$Z = 6.5$; $p = 0.007$**
CGI-S score, median (IQR)	5.0 (4.0–6.0)	2.0 (2.0–3.0)	5.0 (4.0–6.0)	3.0 (2.0–4.0)	$Z = -0.4$; $p = 0.683$	$Z = 25.5$; $p = 0.306$
IPAQ total score, median (IQR)	1206.2 (466.5–3252.0)	1173.0 (582.0–2199.0)	462.0 (231.0–1039.0)	506.5 (41.25–757.5)	$Z = -1.4$; $p = 0.150$	$Z = 2.3$; $p = 0.019$*
PREDIMED-17 total score, mean (SD)	9.0 (2.6)		7.8 (0.8)		$t = -1.9$; $p = 0.330$	
Fagerström total score, median (IQR)	0.0 (0.0–2.0)		3.0 (0.0–6.0)		$Z = -1.6$; $p = 0.112$	
AUDIT total score, median (IQR)	2.0 (1.0–5.0)		0.0 (0.0–2.0)		$Z = -1.7$; $p = 0.082$	
CGI-I total score, median (IQR)		1.0 (1.0–2.0)		2.0 (1.0–2.0)		$Z = -0.6$; $p = 0.612$

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CGI-I, Clinical Global Impression Scale – Improvement; CGI-S, Clinical Global Impression Scale – Severity; FAST, Functioning Assessment Short Test; HDRS, 17-item Hamilton Depression Rating Scale; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; PREDIMED-17, 17-score scale aimed to measure adherence to Mediterranean Diet; SD, standard deviation.

*$p < 0.05$.**$p < 0.01$.

When HC were compared to each patients' subgroup, significant differences were observed in ETC rates when they were compared with bipolar depression ($Z = 1.000$; $p = 0.005$). No other differences were found between controls and manic or depressive patients.

Differences in ETC according to the major medication classes (antidepressants, second-generation antipsychotics, lithium, anticonvulsants and benzodiazepines) were explored, including all participants. No significant differences were found with antipsychotics ($t = -0.942$, $p = 0.355$), benzodiazepines ($t = -0.835$, $p = 0.418$), lithium ($t = -0.429$, $p = 0.671$), or anticonvulsants ($t = 0.083$, $p = 0.935$). No participants were treated with antidepressants.

3.4 | Mitochondrial respiration and HDRS and YMRS items

Mitochondrial respiration was assessed at T0 and T1 according to specific scales items:

i. For HDRS: items 4 (early insomnia), 5 (middle insomnia), 6 (late insomnia), 7 (work and activities) and 8 (psychomotor retardation);
ii. For YMRS: items 2 (increased motor activity or energy), 4 (sleep), 7 (language/thought disorder).

The correlation analyses between scales items and specific OCRs showed that items 7 and 8 of HDRS were negatively correlated with ETC markers at T0 (Rho $= -0.612$, $p = 0.004$; Rho $= -0.587$, $p = 0.007$, respectively), and item 6 with Leak at T0 (Rho $= -0.471$, $p = 0.036$). YMRS item 2 was directly correlated with ETC at T0 (Rho $= 0.456$, $p = 0.043$). At T1, HDRS item 6 and also YMRS items 2 and 7 were directly correlated with ETC (Rho $= 0.548$, $p = 0.012$; Rho $= 0.477$, $p = 0.033$; Rho $= 0.477$, $p = 0.033$, respectively). YMRS item 2 was also correlated with Leak at T1 (Rho $= 0.629$, $p = 0.003$).

Since HDRS insomnia items 4–6, and are scored from 0 to 2, we measured the association with OCRs according to the absence (score 0) or the presence (scores 1 or 2) of the symptom by the OCRs mean comparison between both groups. None of them were associated with a different mean at T0, but at T1 HDRS item 6 was associated with higher ETC rates (39.06 ± 21.42 vs. 21.31 ± 12.83, $p = 0.036$).

For the rest of items, a linear regression was performed, which at T0 showed a tendency for HDRS item 7 to be associated with ETC (OR $= -3.32$, 95%CI –6.72 to 0.77, $p = 0.055$), and a significant association with ETC at T1 with YMRS item 2 (OR $= 19.80$, 95%CI 1.17–38.42, $p = 0.038$).

4 | DISCUSSION

Our results highlight that mitochondrial function might be altered during mood states in BD (both mania and depression), which might revert after clinical remission, and that potential biomarkers that could be identified during manic or depressive phases might not be found in euthymia. Thus, these results suggest that mitochondrial respiratory capacity could be a biomarker of illness activity and clinical response in BD. However, this is a proof-of-concept study with preliminary results that should be confirmed by larger cohorts.

Our longitudinal results showed lower maximal ETC oxygen consumption capacity in acute episodes of BD compared with euthymia after boosting mitochondrial respiration in living PBMC. Interestingly, the overall patients' cohort showed a significant improvement in respiratory capacity from the acute phase to euthymia, although the manic group showed a greater tendency compared to the depressive sample. However, the statistical power might have been influenced by the limited sample size, especially in bipolar depression. The significant results obtained were not influenced by the smoking status. These results should still be interpreted with caution, as they might evidence an ETC dysfunction and thus an impaired aerobic respiration in both manic and depressive episodes of BD, which could be a risk factor for an increased anaerobic respiration and also oxidative stress. Our findings also reveal a potential relationship between energy and activity with maximum mitochondrial respiratory capacity; however, these data should be interpreted with caution given the limited sample size included. Further studies should elucidate whether, as observed in our sample, late insomnia is associated with enhanced mitochondrial respiratory capacity.

Our results did not show significant differences in mitochondrial respiration according to the use of different medication classes, including second-generation antipsychotics, lithium, anticonvulsants and benzodiazepines. Despite these findings suggest pharmacological treatment might not influence mitochondrial function, some previous evidence has reported an impact of different drugs, especially antipsychotics, in mitochondrial activity.[40,41] Hence, future studies should address this relationship deeper.

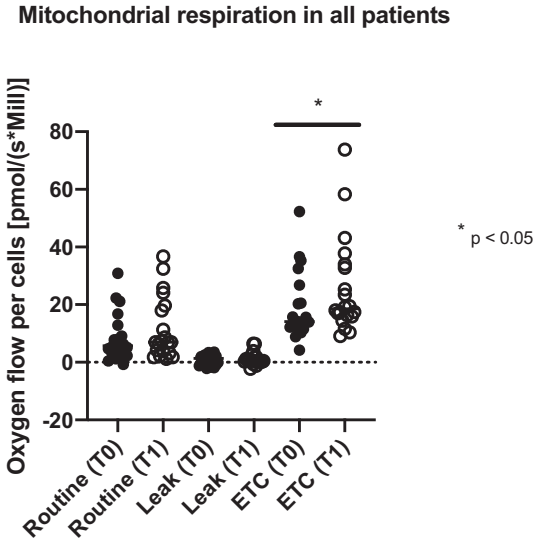

FIGURE 1 Mitochondrial respiration in the overall patients' sample. Filled circles represent acute phases (T0) and empty circles euthymia (T1). Significant differences were observed between T0 T1 in the maximal oxygen consumption capacity (electron transport chain [ETC]) ($p = 0.025$).

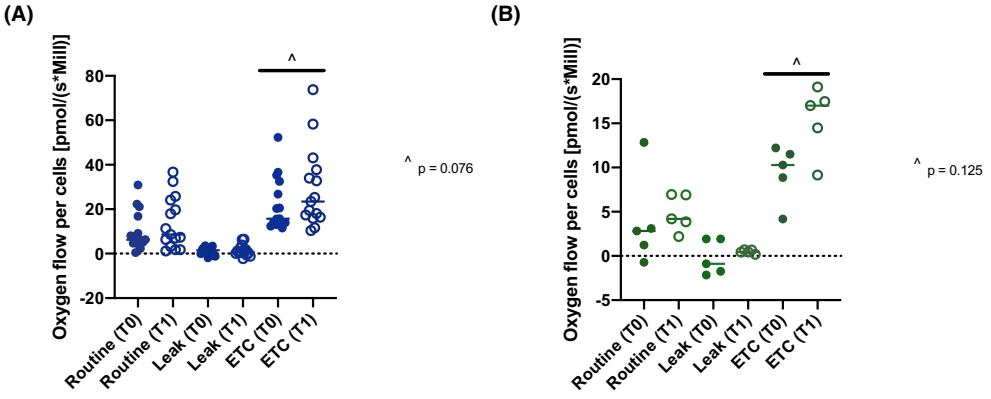

FIGURE 2 Mitochondrial respiration in manic (A) and depressive (B) patients. Filled circles represent acute phases (T0) and empty circles euthymia (T1). A tendency towards an increase in maximal oxygen consumption (electron transport chain [ETC]) was observed in remission (T1) compared to acute mania (T0) ($p = 0.076$) (A). No significant differences were observed between T0 and T1 in depressive patients ($p = 0.125$) (B).

TABLE 3 Estimated mean intra-individual differences in oxygen consumption rates for the overall sample, manic, and depressive patients, corrected for the smoking status.

	Overall sample		Mania		Depression	
	T0–T1		T0–T1		T0–T1	
OCR	Estimated mean difference (CI 95%)	*p* value	Estimated mean difference (CI 95%)	*p* value	Estimated mean difference (CI 95%)	*p* value
Routine	−2.98 (−7.27–1.31)	0.1625	−3.65 (−10.5–3.17)	0.450	−0.97 (−12.8–10.85)	0.996
Leak	−0.39 (−1.73–0.96)	0.556	−0.29 (−2.36–1.78)	0.978	−0.68 (−4.26–2.91)	0.950
ETC	−6.66 (−12.4-[−0.91])	0.0254*	−6.86 (−16.1–2.33)	0.188	−6.04 (−22.0–9.89)	0.711

Abbreviations: ETC, electron transport chain; OCR, oxygen consumption rate.
*$p < 0.05$.

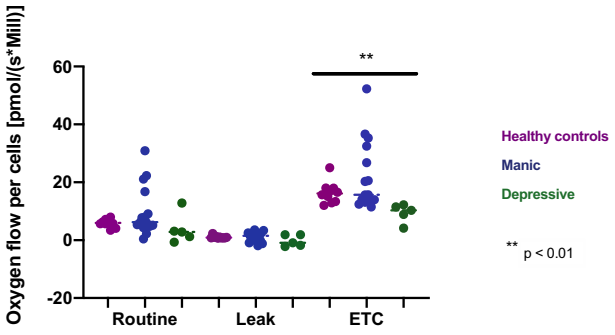

FIGURE 3 Mitochondrial respiration in healthy controls, manic and depressive patients at admission (T0). Significant differences were observed in electron transport chain (ETC) between the three groups ($p = 0.003$).

Lastly, differences derived from the use of antidepressants could not be ruled out due to the lack of participants receiving these medications.

Patients and HC were assessed in the same conditions regarding fasting status, time of the day, sample processing and experimental procedures performed in order to ensure the comparability of the results obtained. Comparisons between acute phases and HC revealed significant differences in ETC rates, mainly due to a reduced maximum OCR in bipolar depression compared to the other groups. Previous studies have similarly reported reduced mitochondrial respiratory capacity in major depressive disorder.[25] These findings need to be further studied and corroborated. However, considering inter-individual variability in mitochondrial function, our results may be interpreted as an improvement in mitochondrial respiratory capacity after achieving symptomatic remission, which should be explained by a potentially normalized mitochondrial function in clinical stability if it is confirmed in future analyses.

Previous research supports the presence of mitochondrial dysfunction in patients with BD. To the authors' knowledge, this is the first study reporting intra-subject longitudinal differences between acute states and clinical remission. In addition, this study examines in vivo PBMC oxygen consumption capacity right after blood extraction and processing. Other studies assessing mitochondrial OCRs in mood disorders have been conducted with smaller samples.[26,27]

The available evidence in the literature is limited by the comparison of patients with BD with HC, the absence of an acute mood episode at the moment of study, and the lack of studies comparing intra-subject OCRs. This is added to the fact that in vivo mitochondrial respiratory capacity has been assessed in smaller cohorts. Moreover, given that mitochondrial function can be assessed at different levels, the methods used in previous evidence to establish the presence of mitochondrial dysfunction differ highly.

In summary, our results suggest that in vivo ETC oxygen consumption capacity may be impaired in acute states of BD compared to clinical remission, even though maximum OCR might not differ substantially from HC. Mitochondrial respiratory capacity might be a state-dependent marker that could be used in the assessment of clinical response in both depressive and manic episodes.

This overarching project aims to assess, in a larger sample, additional mitochondrial markers, such as mitochondrial DNA content in plasma and PBMC and enzymatic activities of the mitochondrial ETC. This will facilitate the correlation of mitochondrial respiration with other mitochondrial parameters and thus the identification of feasible biomarkers of mitochondrial dysfunction that might me associated with clinical severity. This might allow the design of future interventional studies targeting mitochondrial function at specific levels.

Our study comes with some strengths and some limitations. A major strength is the cohort, longitudinal design,[42] which, however, is one of the reasons for the first limitation, the small sample size. Moreover, this

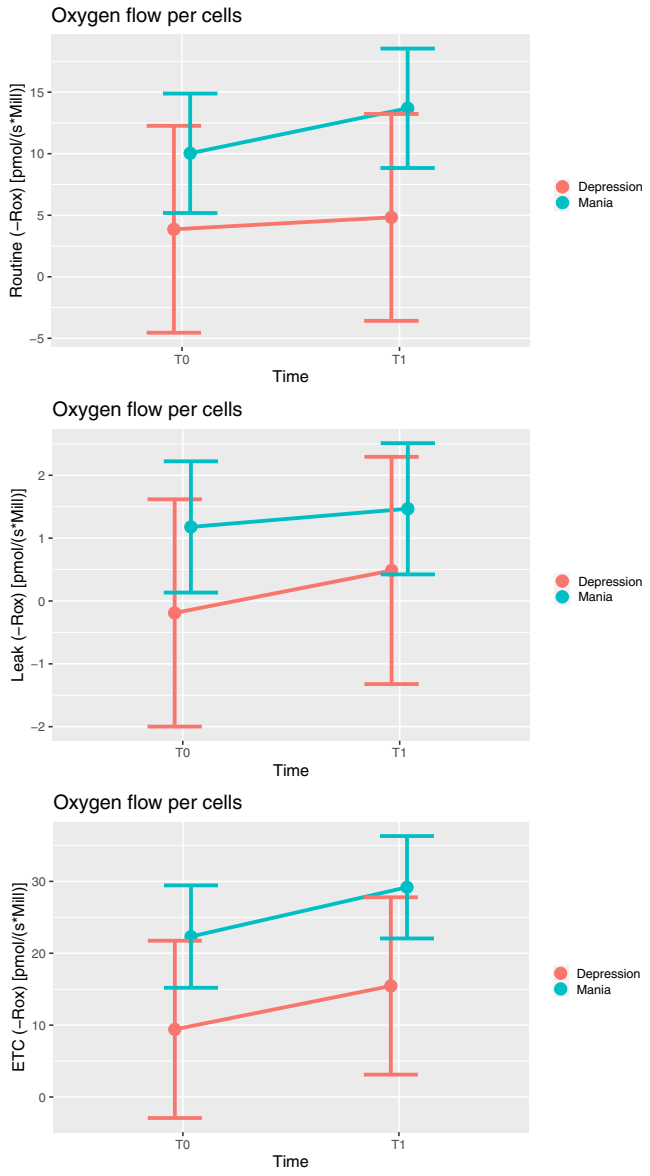

FIGURE 4 Mitochondrial respiration in depressive and manic patients during the acute episode (T0) and after clinical remission (T1). Routine, leak, and electron transport chain (ETC) rates are represented for both groups after Rox deduction. At T0, individuals with bipolar depression showed lower ETC rates than those with a manic episode ($p = 0.001$), which were not significant at T1 ($p = 0.074$).

study included patients who were admitted to an acute psychiatric unit with a short course of disease during high severity acute mood episode requiring admission to an acute psychiatric unit (usually involuntary due to lack of insight), thus guaranteeing the presence of severe mood symptoms and a substantial reduction after remission; as such, the sample obtained is limited and did not include patients with mixed episodes or with a long course of illness. However, compared to previous studies, the sample obtained was larger, and the study design

TABLE 4 Main effects of group, time, and interaction of group and time corrected for the smoking status.

	Mania		Depression		Effect					
	T0	T1	T0	T1	Time		Group		Group × time	
OCR	Mean (CI 95%)	Mean (CI 95%)	Mean (CI 95%)	Mean (CI 95%)	F	*p* value	*F*	*p* value	*F*	*p* value
Routine	10.37 (4.99–15.70)	14.02 (8.65–19.40)	3.72 (−4.98–12.40)	4.68 (−4.02–13.4)	0.92	0.351	3.24	0.090	0.31	0.585
Leak	1.30 (0.20–2.41)	1.59 (0.49–2.70)	−0.24 (−2.07–1.58)	0.43 (−1.39–2.26)	0.43	0.514	3.12	0.086	0.07	0.793
ETC	23.62 (15.82–31.4)	30.48 (22.68–38.30)	8.85 (−3.75–21.5)	14.89 (2.29–27.5)	3.93	0.063	5.37	0.033*	0.02	0.900

Abbreviations: ETC, electron transport chain; OCR, oxygen consumption rate.
*$p < 0.05$.

allowed to perform intra-individual comparisons between two different clinical states. Patients' recruitment and the first mitochondrial respiration assessment were conducted during a severe mood episode, at their admission to our acute unit. In addition, the novel method of obtaining in vivo ETC oxygen consumption capacity with a respirometer differs from most previous evidence that used different methods to address the study of mitochondrial function. The current method allows to assess mitochondrial respiration in fresh, right after the blood extraction, and then requires a link between the inpatient unit and a specialized laboratory. On the other hand, the specific method used to assess mitochondrial respiration in this study was not contrasted with different analyses aimed to measure mitochondrial function in patients with BD. This limits comparability of our study with previous research and also hinders the capacity to reach a conclusion regarding the presence of mitochondrial dysfunction in patients during an acute phase, which should be addressed with further specific analyses. Even though the inpatient unit ensures a lower variability in different environmental conditions, since illicit substances and tobacco are strictly forbidden, caffeine consumption is not allowed and a balanced diet is provided in all cases, other factors, such as pharmacological treatments and other individual characteristics might influence ETC respiration. The effects of treatment cannot be discounted,[43] especially as agents like antipsychotics, which are commonly used in mania, have significant effects on mitochondrial functioning and generally suppress mitochondrial biogenesis.[44,45] Some of these variables (i.e., age, sex) were controlled for. On the other hand, the possibility of obtaining our results at two different times in the same patients during their admission in the acute psychiatric unit allows to reduce potential confusion factors. Also, this research included patients with severe mood episodes that needed an acute admission and who later reached remission, which provides results from two highly different states. Another strength of this study is the fact that laboratory measurements were performed at the same time as the clinical evaluation, since the experiment used requires the assessment of ETC respiratory capacity from living cells right after the blood centrifugation procedure.

Future studies with similar designs and larger samples, including medication-free participants, would be useful in order to progress in this field, contribute to the correlation of different mitochondrial dysfunction parameters and identify state-dependent biomarkers that may in the future open new opportunities for individualized interventions aimed to enhance mitochondrial function.

To conclude, patients with an acute episode of BD showed significantly reduced maximum mitochondrial respiratory capacity compared to those in euthymia. People with manic episodes showed higher levels of mitochondrial oxygen consumption than subjects under a depressive episode, and also higher tendency to restore respiratory capacity at clinical remission. These results underscore the importance of performing intra-individual assessments in the study of mitochondrial function, which could serve as a state-dependent marker. Further studies with similar designs are needed to fully elucidate the relationship between impaired mitochondrial function and patients' characteristics, and also to identify potential biomarkers in different phases of the disease. This could potentially be useful to increase the knowledge around the role of specific interventions in the treatment of acute episodes or in relapse prevention in BD.

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CONFLICT OF INTEREST STATEMENT

AGP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Casen Recordati, LCN, Rovi and Angelini. GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, Rovi, Casen Recordati, and Angelini, with no financial or other relationship relevant to the subject of this article. EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag, and Lundbeck. IG has received grants and served as consultant, advisor or CME speaker for the following identities: Angelini, Casen Recordati, Ferrer, Janssen Cilag, and Lundbeck, Lundbeck-Otsuka, Luye, SEI Healthcare. MB has received grant/research support from National Health and Medical Research Council, Wellcome Trust, Medical Research Future Fund, Victorian Medical Research Acceleration Fund, Centre for Research Excellence CRE, Victorian Government Department of Jobs, Precincts and Regions, and Victorian COVID-19 Research Fund. He received honoraria from Springer, Oxford University Press, Cambridge University Press, Allen and Unwin, Lundbeck, Controversias Barcelona, Servier, Medisquire, HealthEd, ANZJP, EPA, Janssen, Medplan, Milken Institute, RANZCP, Abbott India, ASCP, Headspace and Sandoz (last 3 years). All authors report no financial or other relationship relevant to the subject of this article.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Aerobic capacity and mitochondrial function in bipolar disorder: a longitudinal study during acute phases and after clinical remission

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Background: Aerobic capacity has shown to predict physical and mental health-related quality of life in bipolar disorder (BD). However, the correlation between exercise respiratory capacity and mitochondrial function remains understudied. We aimed to assess longitudinally intra-individual differences in these factors during mood episodes and remission in BD.

Methods: This study included eight BD patients admitted to an acute psychiatric unit. Incremental cardiopulmonary exercise test (CPET) was conducted during acute episodes (T0), followed by constant work rate cycle ergometry (CWRCE) to evaluate endurance time, oxygen uptake at peak exercise (VO_{2peak}) and at the anaerobic threshold. The second test was repeated during remission (T1). Mitochondrial respiration rates were assessed at T0 and T1 in peripheral blood mononuclear cells.

Results: Endurance time, VO_{2peak}, and anaerobic threshold oxygen consumption showed no significant variations between T0 and T1. Basal oxygen consumption at T1 tended to inversely correlate with maximal mitochondrial respiratory capacity (r=-0.690, p=0.058), and VO_{2peak} during exercise at T1 inversely correlated with basal and minimum mitochondrial respiration (r=-0.810, p=0.015; r=-0.786, p=0.021, respectively).

Conclusions: Our preliminary data showed that lower basal oxygen consumption may be linked to greater mitochondrial respiratory capacity, and maximum oxygen uptake during the exercise task was associated with lower basal mitochondrial respiration, suggesting that lower oxygen requirements could be associated with greater mitochondrial capacity. These findings should be replicated in larger samples stratified for manic and depressive states.

KEYWORDS

bipolar disorder, mania, depression, aerobic capacity, endurance time, mitochondrial respiration

Introduction

Bipolar disorder (BD) is a chronic and recurrent disease characterized by depressive and manic or hypomanic mood episodes alternated with periods of euthymia (1). It is associated with reduced functionality and medical comorbidities (1), especially metabolic disorders that impact physical and mental health prognosis (2). Individuals with BD face an elevated risk of premature cardiovascular-related death, attributed in part to a reduced exercise capacity (3).

Exercise tolerance has been widely studied in somatic diseases. Endurance time during constant work rate cycle ergometry (CWRCE), known as the total time the individual maintains exercise at a constant work rate, has been associated with patients' experience of physical functioning in daily life, and considered a useful efficacy endpoint in clinical intervention trials (4). Poor aerobic endurance and muscle strength are associated in mental illnesses, including BD, with impaired physical function, increased risk of lifestyle-related diseases, and early mortality (5). In BD, longer illness duration, higher body mass index (BMI), higher levels of depression and lower physical activity levels have been associated with lower physical fitness, emerging as an eminent modifiable risk factor for somatic comorbidity (3).

Cardiorespiratory fitness, assessed through maximum oxygen uptake (VO_{2peak}), is considered a predictive measure for cardiovascular disease and premature mortality, demonstrating the potential of exercise to counteract compromised physical health in BD (3).

Exercise-induced changes in mitochondrial function, crucial for determining exercise capacity (6), have been explored in various contexts but remain understudied in BD, despite suggestions of mitochondrial dysfunction as a potential marker in the disorder's pathophysiology (7, 8).

No biomarkers have yet been implemented in clinical practice to support diagnostic and therapeutic processes. This study addresses a gap in research by longitudinally assessing intra-individual differences in aerobic capacity and mitochondrial respiration during different mood states in BD patients. We primarily hypothesized a positive correlation between aerobic capacity and mitochondrial respiration in BD, and secondarily an improvement in both after clinical remission compared to the acute episode. Therefore, we aimed to study the association between respiratory capacity during physical activity and mitochondrial respiration, measured after the extraction of peripheral blood mononuclear cells (PBMC), across the different states of the illness, and also longitudinally determine differences in the aerobic capacity and oxygen uptake between the acute mood episodes and remission. Finally, we studied the association between aerobic capacity with BMI and physical activity.

Methods

Study design and population

The current work, derived from a financed longitudinal study (PI21/00169), aimed to assess intra-individual differences in oxygen consumption, exercise capacity and mitochondrial function longitudinally in patients with BD (9).

Adult inpatients admitted to our acute psychiatric unit with BD type I with an acute manic or depressive episode, according to DSM-5 criteria (10), were eligible for this study. Assessments occurred during the acute episode (T0) and after symptomatic remission (T1), defined as standardized clinical scores ≤7 at the Young Mania Rating Scale (YMRS) (11) or the 17-item Hamilton

Depression Rating Scale (HDRS) (12) (i.e. symptoms absent or nearly absent), before hospital discharge. A disease course shorter than ten years was necessary for patient recruitment. Patients with intellectual quotient lower than 80, with substance use disorders other than tobacco and cannabis, and with any cardiac, respiratory, auto-immune, inflammatory illness or with an acute infectious illness were excluded from this study, as well as those with known history of familial mitochondrial disease.

The capacity to provide informed consent was assessed before entering the study and re-assessed after remission. This study was approved by the Hospital Clínic Research Ethics Committee (HCB/2021/0358).

Clinical evaluation

Socio-demographic and clinical data were collected. Lung function was assessed with forced spirometry and diffusing lung capacity for carbon monoxide (DLCO), to exclude any respiratory limitations (13). Manic and depressive symptoms were assessed respectively using standardized psychometric scales: YMRS (11) and HDRS (12). Functioning was assessed with Functioning Assessment Short Test (FAST) (14), disease severity with Clinical Global Impression Scale – Severity (CGI-S) (15), and physical activity with International Physical Activity Questionnaire (IPAQ) (16), and adherence to Mediterranean diet with a 17-score scale (PREDIMED-17) (17). At T1, CGI-Improvement (CGI-I) scale was obtained, and HDRS, YMRS, FAST, IPAQ, CGI-S were re-administered. Clinical variables were assessed at T0 and T1.

Assessment of aerobic capacity

At T0, patients were evaluated with an incremental CPET, and then with a CWRCE (18), both conducted on a cycle ergometer (Lode Corival CEPT mod:960900, Groningen, The Netherlands). During the CWRCE, patients performed the test at the 80% of the peak work-load achieved in the incremental CPET. The CWRCE was also conducted at T1.

In the CWRCE, endurance time in seconds, an indicator of aerobic capacity (6), VO_{2peak} and oxygen uptake at the anaerobic threshold in L/min were measured. The last was obtained as an expression of the exercise intensity indicating the transition from mild to moderate exercise and from aerobic to anaerobic work intensity. The association between the aerobic capacity with BMI and physical activity was studied to assess the influence of non-psychiatric factors, such as physical fitness and exercise routines, in exercise performance.

Assessment of mitochondrial respiration

Mitochondrial oxygen consumption rates (OCRs) were assessed at T0 and T1, after the isolation of peripheral blood mononuclear cells (PBMC) obtained by a Ficoll density gradient centrifugation procedure. To determine OCRs at T0 and T1, a million living PBMCs resuspended in PBS1x were used. High-resolution respirometry was conducted in fresh cells at 37°C by polarographic oxygen sensors in a two-chamber Oxygraph-2k system (OROBOROS Instruments, Innsbruck, Austria). Specific OCRs were obtained (Routine: basal oxygen consumption with no exogenous substrates; Leak: oxygen consumption not coupled to ATP synthesis; ETC: maximal capacity of the electron transport chain; and Rox: oxygen consumption not linked to mitochondrial activity). Routine, Leak and ETC OCRs were registered by subtracting the rates from Rox as it is considered unspecific and non-mitochondrial oxygen consumption. The following inhibitors and uncouplers were manually injected: (i) oligomycin (1.5 mM), an ATP synthase inhibitor, (ii) carbonyl cyanide 3-chlorophenylhydrazone (CCCP) (1 mM), a mitochondrial uncoupler, and (iii-iv) rotenone (2 mM) and antimycin A (0.2 mM), which are complex I and complex III inhibitors, respectively.

Oxygen uptake was normalized per million cells. Results are expressed as picomoles of oxygen per million cells (pmol O_2/million).

Statistical analysis

Statistical analyses were computed with 'IBM SPSS Statistics 25' and GraphPad Prism. Quantitative variables were summarized as median and interquartile range (IQR), and categorical variables as frequencies. For intra-subjects' comparisons, Wilcoxon matched-pairs signed rank tests were used. Spearman test was used for correlation analyses. Results were controlled for pharmacological treatment. Statistical significance level was set at $p<0.05$.

Results

Table 1 outlines the key characteristics of the 8 participants (6 manic, 2 depressed) included.

Compared to patients with a manic episode, those with a depressive episode presented higher HDRS total score at admission (25.0 ± 11.3 vs 4.0 ± 2.7), with no major differences at endpoint. As expected, those with a manic episode displayed higher YMRS total score at admission compared to depressive patients (23.5 ± 10.5 vs 1.5 ± 2.1), which partially reduced at discharge (4.8 ± 2.0 vs 0.0 ± 0.0). In addition, relevant differences were found between groups in FAST total score at admission (13.3 ± 8.5 in mania vs 37.5 ± 3.5 in depression) and after clinical remission (6.0 ± 7.1 in mania vs 29.5 ± 4.9 in depression), with no major differences in CGI, IPAQ or PREDIMED-17 scales scores.

Spirometry was performed in all patients to assess resting pulmonary capacity, which was within reference values in all cases.

Intra-subject longitudinal comparisons between acute mood episodes (T0) and clinical remission (T1) for the overall patients' sample are shown in Figure 1.

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TABLE 1 Socio-demographic and clinical characteristics of the sample.

	Mania	Depression
	n = 6 (75%)	n = 2 (25%)
Sex, n females (%)	4 (66.7)	1 (50.0)
Age, mean (SD)	24.2 (4.4)	33.5 (9.2)
BMI (T0), mean (SD)	21.0 (1.2)	22.7 (1.9)
Abdominal circumference (T0), mean cm (SD)	76.7 (5.3)	92.0 (8.5)
Number of total previous episodes, mean (SD)	1.8 (1.2)	3.5 (2.1)
Months from onset of first affective episode, mean (SD)*	48.3 (36.5)	192.0 (67.9)
Age of onset of BD, mean (SD)	22.2 (5.2)	30.5 (13.4)
Age at first hospitalization, mean (SD)	22.0 (4.5)	28.0 (17.0)
Number of previous psychiatric hospitalizations, mean (SD)	1.0 (1.3)	2.5 (3.5)
Number of previous manic episodes, mean (SD)	0.5 (1.2)	1.0 (1.4)
Number of previous depressive episodes, mean (SD)	0.8 (1.0)	2.5 (0.7)
Previous psychiatric diagnosis, n (%)	4 (66.7)	2 (100)
Previous psychiatric medication, n (%)	3 (50.0)	2 (100)
Current psychiatric follow-up, n (%)	3 (50.0)	2 (100)
Life stressor, n (%)	2 (33.3)	0 (0.0)
Psychotic symptoms, n (%)	5 (83.3)	0 (0.0)
Delusions, n (%)	4 (66.7)	0 (0.0)
Hallucinations, n (%)	2 (33.3)	0 (0.0)
Previous suicide attempt, n (%)	1 (16.7)	1 (50.0)
Cannabis use, n (%)	4 (66.7)	0 (0.0)
Somatic illness, n (%)	1 (16.7)	0 (0.0)
Family psychiatric history, n (%)	4 (66.7)	2 (100)
Family history of BD, n (%)	1 (16.7)	1 (50.0)
Treatment discontinuation, n (%)	2 (33.3)	0 (0.0)
Living alone, n (%)	1 (16.7)	1 (50.0)
Higher education, n (%)	1 (16.7)	2 (100)
Working activity, n (%)	3 (50.0)	2 (100)

SD, standard deviation; BD, bipolar disorder. *Significant at $p<0.05$.

No significant differences between T0 and T1 were found in the endurance (p=0.779), VO_{2peak}, (p=0.779) or oxygen consumption at the anaerobic threshold (p=0.726).

All patients included had normal weight (median: 21.20 kg/m^2, IQR: 20.39-22.61). However, patients' BMI tended to be directly correlated with endurance time at T1 (r=0.667, p=0.071). IPAQ total score at T0 was associated with more prolonged endurance time (r=0.905, p=0.005).

Despite mitochondrial respiratory capacity showed a tendency to increase at T1 compared to T0, differences in the different OCRs were not significant.

Endurance time at T0 or T1 did not show any association with mitochondrial respiratory capacity. Likewise, at T0, no relevant correlations were observed between oxygen uptake during the effort test and mitochondrial oxygen consumption. Nevertheless, at T1, basal oxygen consumption (before starting CWRCE) tended to be inversely correlated with maximum mitochondrial respiratory capacity (ETC) (r=-0.690, p=0.058). In addition, VO_{2peak} at T1 was inversely correlated with Routine (r=-0.810, p=0.015) and Leak (r=-0.786, p=0.021) OCRs.

Discussion

In this preliminary study, no significant differences were found in aerobic capacity, including endurance time, VO_{2peak} or oxygen consumption at the anaerobic threshold during CWRCE, or mitochondrial respiration between severe acute mood states and after clinical remission, although the second showed a tendency to increase in clinical remission compared to the acute states, which is supported by recent results from our group (9). An inverse association was noted between basal oxygen consumption and maximum mitochondrial respiratory capacity after remission, suggesting individuals with increased mitochondrial capacity might have lower basal oxygen requirements and higher mitochondrial efficiency, which should be confirmed in larger samples.

In addition, the maximum oxygen uptake during CWRCE at clinical remission was inversely correlated with basal mitochondrial respiration, suggesting physical fitter individuals may exhibit lower resting mitochondrial oxygen requirements. Our results suggest an association between an electron transport chain dysfunction and an impaired aerobic respiration, which could be a risk factor for an increased anaerobic respiration and oxidative stress.

Higher BMI tended to be correlated with longer endurance time after clinical remission, hinting a better physical fitness in this cohort. Also, IPAQ total score was associated with more prolonged endurance time during the acute state, revealing a stronger association of endurance capacity with physical fitness rather than with the severity of the acute episode.

To the authors' knowledge, this is the first study reporting intra-subject longitudinal differences in BD between acute states and clinical remission and aiming to find a potential association between oxygen consumption capacity during an effort test and mitochondrial respiration. Other studies assessing mitochondrial OCRs in mood disorders have been conducted with smaller samples (19, 20).

The study strengths include intra-individual comparisons between clinical states in patients with short course of illness and severe episodes, larger samples compared to previous studies, and *in vivo* mitochondrial respiratory capacity assessment. Also, laboratory measurements were performed at the same time as the clinical evaluation and the effort tests in the cycle ergometer were obtained. Limitations include the small sample size, explained by

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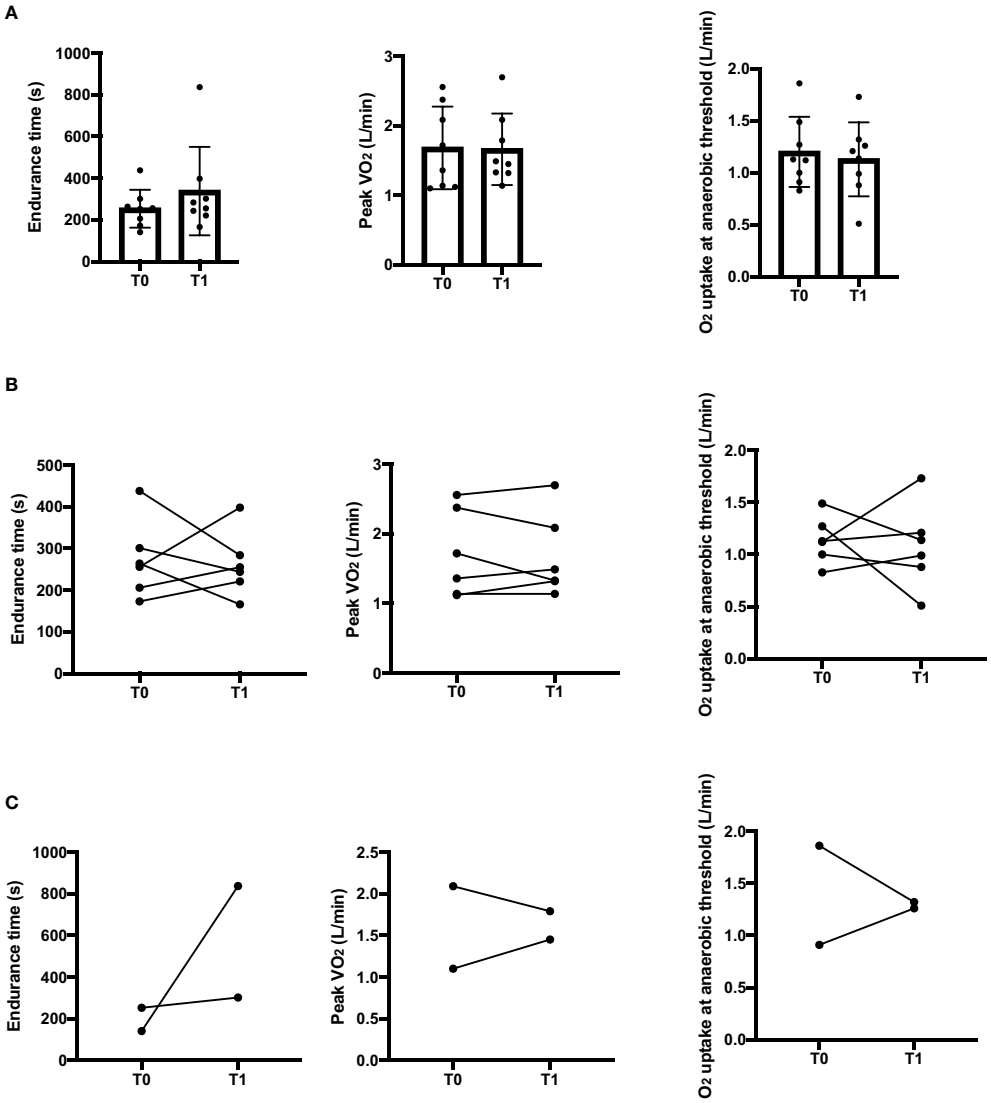

FIGURE 1
Intra-subject comparisons in endurance time, peak oxygen uptake and oxygen uptake at the anaerobic threshold between the acute state (T0) and clinical remission (T1) for the overall sample **(A)**, for manic patients **(B)** and for depressive patients **(C)** in the constant work rate cycle ergometry. s, seconds; L, liters.

the severity of mood episodes, which hindered recruitment. The small sample size did not allow differentiation from participants at index mania and index depression, which might be expected to differ. Finally, even though the inpatient unit ensures a lower variability in different environmental conditions, since illicit substances and tobacco are strictly forbidden, and a balanced diet is provided in all cases, other factors, such as some individual characteristics, might have influenced mitochondrial respiration.

In conclusion, our results suggest that impaired mitochondrial oxygen consumption capacity may be reflected by exercise performance, and that physical fitness might predict a better exercise performance over the illness' state, whereas mitochondrial respiratory capacity might increase in clinical remission compared to the acute states. Further studies should elucidate aerobic exercise could enhance mitochondrial respiratory capacity, whether this could be used as a state-dependent marker in the assessment of clinical response, and if the enhancement of physical activity might be a potential strategy to prevent not only metabolic comorbidities, but also mitochondrial dysfunction, which might pave the way for personalized interventions in BD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Hospital Clinic Research Ethics Committee (HCB/2021/0358). The studies were

conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. MG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. GR: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. ES: Investigation, Supervision, Visualization, Writing – review & editing. RB: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. AM: Investigation, Methodology, Project administration, Resources, Writing – review & editing. FG: Conceptualization, Data curation, Investigation, Resources, Visualization, Writing – review & editing. ET: Investigation, Methodology, Resources, Supervision, Writing – review & editing. LV: Resources, Supervision, Visualization, Writing – review & editing. GA: Conceptualization, Methodology, Software, Supervision, Writing – review & editing. MV: Conceptualization, Methodology, Visualization, Writing – review & editing. LO: Project administration, Visualization, Writing – review & editing. Od: Project administration, Visualization, Writing – review & editing. IO: Project administration, Visualization, Writing – review & editing. HA: Project administration, Visualization, Writing – review & editing. JR: Conceptualization, Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. NV: Conceptualization, Supervision, Visualization, Writing – review & editing. MB: Conceptualization, Data curation, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing. EV: Conceptualization, Supervision, Visualization, Writing – review & editing. GG: Writing – review & editing, Writing – original draft. JR: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Validation, Visualization. XA: Conceptualization, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing, Project administration, Resources. IP: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing, Funding acquisition, Writing – original draft.

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Conflict of interest

AG-P has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Casen Recordati, LCN, Rovi and Angelini. GA has received CME-related honoraria, or consulting fees from Angelini, Casen Recordati, Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, and Rovi, with no financial or other relationship relevant to the subject of this article. EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag, and Lundbeck. IG has received grants and served as consultant, advisor or CME speaker for the following identities: Angelini, Casen Recordati, Ferrer, Janssen Cilag, and Lundbeck, Lundbeck-Otsuka, Luye, SEI Healthcare.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Analyzing Nutritional and Metabolic Factors for Predicting Malnutrition and Readmission Following a Manic Episode in Bipolar Disorder: A Machine Learning Approach

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Abstract

Background: Pharmacological treatments, lifestyle habits and the mental illness by itself entail a higher risk for a poorer nutritional status in bipolar disorder (BD). This study aims to determine the impact of metabolic and nutritional parameters on the course of illness.

Methods: Adult patients admitted to the Hospital Clínic of Barcelona acute unit with a manic episode from 2015 to 2019 were included in this longitudinal study. Sociodemographic, clinical, nutritional and metabolic variables and prognostic factors at three years were collected. A random forest model was used to determine predictors of readmission and malnutrition.

Results: Readmission was seen in 36.2% of the 279 individuals included. LDL cholesterol levels were associated with the number of readmissions (p=0.005). LDL cholesterol and leucocyte count were associated with the number of emergency visits (p=0.003 and p=0.007, respectively), as well as the LDL/HDL ratio and the atherogenic coefficient (p=0.015 and p=0.048, respectively). Higher LDL cholesterol levels, BMI and leucocyte count were associated with shorter time to readmission (p=0.025, p=0.019 and p=0.036, respectively), and also lower fasting glucose levels (p=0.031). The machine learning model showed a strong predicting value for malnutrition, which was lower for readmission.

Conclusions: Our results suggest that BMI, LDL cholesterol and leucocyte count, but not malnutrition risk, might influence the psychiatric prognosis. The machine learning algorithm demonstrated a high potential for predicting malnutrition. These findings might allow the identification of profiles of patients who could benefit from lifestyle interventions.

Keywords: bipolar disorder, malnutrition, nutritional status, body mass index, manic episode, readmission; machine learning.

Word count: 4419 words.

Introduction

Bipolar disorder (BD) is a chronic and recurrent illness characterized by the presence of depressive, manic, hypomanic or mixed episodes alternated with periods of euthymia (1,2). Even when receiving proper treatment, patients with BD can suffer long-term consequences, such as reduced functionality, impaired quality of life or cognition, or medical comorbidities (2).

In severe mental illnesses, physical health is often compromised, with an increased prevalence of cardiovascular diseases and a reduced life expectancy compared to the general population (301–303). Patients with BD are considered at high risk to present metabolic and other somatic conditions, and these have been associated with an impaired course of the psychiatric illness (111). Higher mean body mass index (BMI) and waist circumference have been described in BD population compared to healthy controls (304,305). Other evidence has shown higher levels of cardiometabolic risk indicators in patients with BD compared to controls, including waist-to-hip ratio, BMI and non-HDL cholesterol (306). The atherogenic coefficient, measured as non-HDL cholesterol/HDL cholesterol, has also been seen increased in patients with BD compared to healthy controls (307). Some medications, such as second-generation antipsychotics, have also been associated with higher total cholesterol and triglycerides levels, weight gain and increased fasting glucose (308,309).

On the other hand, hospital malnutrition is a prevalent problem that affects up to 50% of both medical and surgical patients (76,77), defined as a state resulting from lack of intake or uptake of nutrients that leads to altered body composition, such as decreased fat free mass, and body cell mass leading to diminished physical and mental function and, eventually, impaired clinical outcomes (73). Some studies have reported that malnutrition at admission can increase patient's morbidity and mortality as well as healthcare expenses (76–79). People with severe mental illnesses are often in poor physical health, which increases risk of malnutrition and impacts mortality rates and life expectancy (310).

Some of the available literature aimed at the assessment of nutritional status in patients with different somatic illnesses uses the controlling nutritional status (CONUT) score, which considers the total lymphocyte count, serum albumin, and total cholesterol levels.

This tool has shown a relationship with medical prognosis in different tumors, hematological malignancies and heart diseases (311–314). Notwithstanding, these studies often exclude psychiatric patients (78,79,315,316) and, with the exception of population with eating disorders (317), evidence regarding the implications of nutritional status in somatic or psychiatric clinical outcomes in patients with mental illnesses is limited (318). In addition, despite cannabis use has shown appetite-stimulating effects (319), its impact on nutritional status is still unknown.

The acknowledgment of patients' nutritional status in BD might help elucidate its relationship with different factors, such as the illness by itself, lifestyle habits, pharmacological treatments and medical and psychiatric prognosis. As an example, during depressive episodes, patients with BD can present reduced appetite and weight loss (302), which can be added to a limited availability of healthy food, inadequate social support, a low socio-economic status among others which could in turn affect their prognosis (320,321).

Previous evidence has shown that metabolic syndrome and related components are associated with worse psychiatric outcomes, including a chronic course of illness, rapid cycling and worse global and cognitive functioning (111). Higher BMI, obesity and lower bilirubin serum levels have been associated with higher prevalence of suicide attempts, medical comorbidities and a more severe psychiatric illness (322,323).

Acute psychiatric hospitalizations often include the assessment of metabolic status and blood tests that measures cholesterol and total protein levels and lymphocyte count, which can be used for the assessment of the patients' nutritional status. Nevertheless, there is a lack of evidence considering the impact of the nutritional status in patients with BD in short- or long-term prognostic factors.

Some studies have shown the feasibility of developing predictive models in mental health through machine-learning algorithms (324–326). However, to the best of our knowledge, no study has applied machine-learning techniques to date to predict malnutrition or prognosis from nutritional parameters in patients with BD.

This study aims to provide a first approach to evaluate in patients with BD the relationship

between nutritional status and the psychiatric prognosis, such as the number of emergency visits, acute readmissions and time to relapse. Secondary aims of this study include the identification of factors associated with hospital readmission after a three-year follow-up period in patients with BD admitted to an acute psychiatric ward with a manic episode, the characterization of the nutritional status of these patients, and the potential of nutritional variables to predict malnutrition and readmission in BD through the use of a random forest (RF) model.

Methods

2.1. Participants

The data analyzed were derived from records corresponding to patients aged 18 years or older admitted to the Hospital Clínic of Barcelona acute psychiatric ward with a manic episode from January 1st 2015 to December 31st 2019, with a follow-up period of three years after the index admission. Ethical approval was provided by the Hospital Clínic Research Ethics Committee (protocol code: HCB/2022/1259).

Patients from whom no nutritional parameters were available at the beginning of the hospitalization were excluded from the study. Patients with more than one admission in the assessed period were included only once, considering the earliest admission. No restrictive criteria were established in terms of psychiatric comorbidities, being all patients admitted in the acute psychiatric ward with a manic episode considered for inclusion.

2.2 Variables assessment

2.2.1. Sociodemographic and Clinical Measures

Some of the variables collected for analysis included age, gender, length of stay, the presence of medical conditions, psychiatric comorbidities, cannabis use, and personal and family history. Variables regarding treatment included pharmacological treatment previous to admission and at discharge. The numbers of emergency visits and

readmissions at three years from the index admission were also collected, as well as the time until the first readmission.

2.2.2. Nutritional and Metabolic Measures

The nutritional status was assessed at admission with the CONUT score, which takes into account the total lymphocyte count, serum albumin, and total cholesterol levels. Total scores between 0 and 1 were considered normal, 2-4 mild malnutrition, 5-8 moderate malnutrition and 9-12 severe malnutrition (16). Thus, risk of malnutrition was considered when CONUT score was 2 or higher.

Other collected variables were BMI, fasting glucose, creatinine, uric acid, total cholesterol, LDL and HDL cholesterol, triglycerides, AST, ALT, GGT, total bilirubin, alkaline phosphatase, total proteins, prealbumin, sodium, potassium, calcium, phosphorus, magnesium, zinc, haemoglobin, platelets, thyroid-stimulating hormone (TSH), vitamin B_{12}, folic acid and vitamin D_3. Finally, as main indicators of cardiovascular risk, we calculated LDL/HDL cholesterol ratio and the atherogenic coefficient, measured as (total cholesterol – HDL cholesterol)/HDL cholesterol.

2.3 Statistical Analyses

In the descriptive analysis, quantitative variables were expressed by mean and standard deviation (SD). Results from categorical variables were shown as frequencies with percentages.

T-tests were used for mean comparisons between two groups when data were normally distributed, and Mann-Whitney U tests were used when they were not. Chi-square tests were used for the comparison of categorical variables.

For the correlation of nutritional parameters with the number of readmissions or emergency visits and for the identification of predictive parameters, linear regression was used after correlation analyses. To calculate the association of malnutrition with nutritional parameters, logistic binary regression analyses were conducted.

A *p*-value<0.05 was used for the screening covariates. Forward stepwise selection algorithms were used for selecting the covariates in the multivariate logistic regression model. At each step, the least significant variable was discarded from the model. Only covariates with a *p*-value <0.10 remained in the final model. These results were contrasted with backward stepwise selection in order to find potential changes in the results. The odds ratio and 95% confidence limit were calculated too. Survival analyses were performed to find the influence of determined parameters in time to relapse requiring hospitalization.

We performed two RF using the R package "RandomForest" (327). RF is a potent predictive tool, known for its proficiency in mitigating bias and robustness against overfitting (327). RF is an extension of the bagging method, that creates diverse decision trees using random subsets of instances and features drawn from the original training dataset. We conducted a first RF considering the readmission at three years as the predicted condition and a second RF considering malnutrition as the predicted condition in the total sample.

First, data from diverse parameters, such as age, laboratory test results, and demographic information, were selected and imputed using multiple imputation techniques to handle missing values. Therefore, we included only the variables presenting at least 80% of the available data in the model.

A 10-fold cross-validation approach was applied to ensure the robustness of the model. Continuous variables were treated as predictors in the RF models. The RF models were trained on a training dataset, with 70% of the data, and subsequently tested on a separate testing dataset. The model's performance was evaluated using metrics such as accuracy, precision, recall, and the F1-score. Additionally, variable importance was assessed to identify the key predictors contributing to the model's performance.

All statistical analyses were performed by the use of a confidence interval of 95%, and significance was set at p<0.05. Analyses were conducted with SPSS version 25.0 (328), GraphPad Prism version 8.4.0 (329), and with RStudio, R version 4.1.2 (330), employing libraries like 'randomForest,' 'mice,' and 'caret' for modeling, imputation, and cross-validation, respectively."

Results

3.1 Characteristics of the sample

A total of 279 individuals admitted to the acute psychiatric ward with a manic episode were included in the study. Socio-demographic and clinical characteristics of the whole sample are available in **Table 1**.

Table 1. Socio-demographic and clinical characteristics of the sample according to the presence or absence of hospital readmission to an acute psychiatric unit during a 3-year follow-up.

	No readmission n = 178 (63.8%)	**Readmission** n = 101 (36.2%)	**Test; p-value** n =279
Sex (% females)	52.8	49.5	$\chi^2 = 0.28$; p =.620
Age, mean (SD)	44.3 (17.0)	45.0 (15.9)	t = -0.44; p =.654
Days of hospitalization, mean (SD)	18.7 (10.9)	21.1 (11.5)	t = -1.74; p =.083
Previous psychiatric history (%)	84.8	96.0	$\chi^2 = 8.20$; p =.002**
Previous diagnosis of BD (%)	52.8	72.3	$\chi^2 = 10.16$; p =.001**
Psychiatric comorbidity (%)	40.7	46.5	$\chi^2 = 0.90$; p =.205
Somatic comorbidity (%)	41.6	46.5	$\chi^2 = 0.65$; p =.249
Previous acute admission (%)	65.0	83.2	$\chi^2 = 10.47$; p =.001**
Lifetime ECT (%)	6.7	13.9	$\chi^2 = 3.87$; p =.042*
Recent life event (%)	25.0	23.2	$\chi^2 = 0.11$; p =.432
Family history of BD (%)	14.2	24.7	$\chi^2 = 4.63$; p =.025*
Previous psychiatric medication (%)	69.1	89.0	$\chi^2 = 14.00$; p =.000**
Cannabis use (%)	28.1	28.7	$\chi^2 = 0.01$; p =.509
Previous psychiatric follow-up (%)	52.5	81.2	$\chi^2 = 22.63$; p =.000**
Number of previous manic episodes, mean (SD)	1.6 (2.3)	3.0 (3.9)	t = -3.18; p =.002**
Number of previous depressive episodes, mean (SD)	1.2 (1.9)	2.5 (4.5)	t = -2.51; p =.013*
Number of previous psychiatric admissions, mean (SD)	2.0 (2.4)	3.7 (3.6)	t = -4.121; p =.000**
Number of previous manic episodes requiring admission, mean (SD)	1.4 (2.0)	2.3 (2.8)	t = -2.99; p =.003**
Number of previous depressive episodes requiring admission, mean (SD)	0.3 (0.8)	0.7 (1.5)	t = -2.49; p =.014*
Psychotic symptoms (%)	75.3	71.3	$\chi^2 = 0.53$; p =.277
Previous treatment			
Antipsychotics (%)	48.3	69.3	$\chi^2 = 11.52$; p =.000**
Antidepressants (%)	24.9	19.8	$\chi^2 = 0.93$; p =.376
Mood stabilizers (%)	39.9	63.4	$\chi^2 = 14.22$; p =.000**
Benzodiazepines (%)	21.9	32.0	$\chi^2 = 3.43$; p =.045*
LAI (%)	7.9	11.9	$\chi^2 = 1.23$; p =.185

Treatment at discharge			
Antipsychotics (%)	97.8	96.0	$\chi^2 = 0.68$; p =.318
Antidepressants (%)	4.5	5.9	$\chi^2 = 2.07$; p =.355
Mood stabilizers (%)	88.8	91.1	$\chi^2 = 0.37$; p =.347
Benzodiazepines (%)	37.7	42.6	$\chi^2 = 1.34$; p =.516
LAI (%)	26.4	30.7	$\chi^2 = 0.59$; p =.264
Emergency psychiatric consultation during follow-up (%)	22.7	96.0	$\chi^2 = 135.96$; p =.000**

SD: standard deviation; IQR: interquartile range; ECT: electroconvulsive therapy; AUD: alcohol use disorder; BMI: body mass index.

No significant differences in age or sex were found between patients with and without psychiatric readmissions after three years. Patients who had previously been diagnosed with BD were 72.3% of those who were rehospitalized and 52.8% of those who had not been readmitted after three years ($\chi^2 = 10.16$; p =.001). The percentages of previous acute admissions were 83.2% in the first group and 65.0% in non-readmitted patients. Patients with readmission during the follow-up period were more likely to be treated previously to the index admission with antipsychotics (p <0.001), mood stabilizers (p <0.001) and benzodiazepines (p =0.045).

3.2 Main findings

3.2.1 Hospital readmission

After a three-year follow-up, 36.2% of patients were readmitted to a psychiatric hospitalization unit with an acute mood episode, and 17.0% of the whole sample had at least two psychiatric readmissions during that period.

The mean number of psychiatric readmissions was 1.95 ± 1.43. In the group with no readmissions, the mean number of emergency psychiatric visits during the follow-up period was 0.53 ± 1.83, whereas in the group requiring rehospitalization it was 3.56 ± 3.81 (t = -7.43, p <0.001). Patients with hospital readmission were also more likely to

attend the emergency psychiatric unit in the following three years after the first admission compared to those not readmitted ($\chi^2 = 135.96$; $p < 0.001$).

3.2.2 Nutritional status

Nutritional characteristics according to the readmission status are represented in **Table 2**. Significant differences were found between readmitted and non-readmitted patients in fasting glucose levels (89.7 ± 12.7 vs 100.6 ± 36.0, $p < 0.001$) and leucocyte count (7.8 ± 2.6 vs 7.2 ± 2.5, $p = 0.042$).

Table 2. Metabolic and nutritional parameters according to the presence or absence of hospital readmission to an acute psychiatric unit during a 3-year follow-up.

	No readmission n = 178 (63.8%)	**Readmission** n = 101 (36.2%)	**Test; p-value** n =279
BMI, mean kg/m^2 (SD)	25.3 (4.8)	27.1 (5.8)	t = -2.32; p =.021*
Obesity (%)	14.8	24.3	χ^2 = 2.91; p =.095
Blood test parameters			
Glucose, mean mg/dL (SD)	100.6 (36.0)	89.7 (12.7)	t = 3.66; p =.000***
Creatinine, mean mg/dL (SD)	0.8 (0.2)	0.8 (0.3)	t = -0.15; p =.0884
Uric acid, mean mg/dL (SD)	5.7 (1.8)	5.7 (1.5)	t = -0.12; p =.904
Cholesterol, mean mg/dL (SD)	165.2 (38.3)	169.0 (36.3)	t = -0.71; p =.480
LDL cholesterol, mean mg/dL (SD)	87.8 (24.9)	98.1 (34.7)	t = -1.82; p =.072
HDL cholesterol, mean mg/dL (SD)	45.2 (14.0)	50.6 (15.7)	t = -1.92; p =.057
Triglycerides, mean mg/dL (SD)	111.9 (72.4)	113.7 (59.2)	t = -0.19; p =.849
AST, mean U/L (SD)	30.5 (33.1)	29.2 (35.3)	t = 0.28; p =.779
ALT, mean U/L (SD)	26.4 (20.7)	30.9 (53.2)	t = -0.93; p =.352
GGT, mean U/L (SD)	32.3 (48.8)	29.1 (36.1)	t = 0.50; p =.618
Total bilirrubin, mean mg/dL (SD)	0.6 (0.7)	0.6 (0.3)	t = 0.24; p =.807
Alkaline phosphatase, mean U/L (SD)	73.3 (28.9)	73.4 (26.5)	t = -0.03; p =.973
Total proteins, mean g/L (SD)	67.9 (8.1)	66.9 (6.6)	t = 0.96; p =.338
Albumin, mean g/L (SD)	42.1 (3.5)	42.2 (4.9)	t = -0.23; p =.815
Prealbumin, mean g/L (SD)	0.2 (0.1)	0.2 (0.1)	t = -0.28; p =.778
Sodium, mean mEq/L (SD)	141.7 (2.6)	141.6 (3.7)	t = 0.31; p =.756
Potassium, mean mEq/L (SD)	4.3 (0.4)	4.3 (0.4)	t = 0.32; p =.747
Calcium, mean mg/dL (SD)	9.3 (0.9)	9.4 (0.6)	t = -1.31; p =.190
Phosphorus, mean mg/dL (SD)	3.8 (0.6)	3.8 (0.6)	t = 0.07; p =.945
Magnesium, mean mg/dL (SD)	2.1 (0.2)	2.1 (0.2)	t = 0.31; p =.757
Zinc, mean µg/dL (SD)	91.2 (17.8)	90.4 (17.1)	t = 0.31; p =.760
Leucocytes, mean n·10^9/L (SD)	7.2 (2.5)	7.8 (2.6)	t = -2.05; p =.042*
Haemoglobin, mean g/L (SD)	138.5 (15.0)	138.9 (13.9)	t = -0.21; p =.838
Platelets, mean n·10^9/L (SD)	239.7 (69.4)	249.5 (70.3)	t = -1.13; p =.260
TSH, mUI/L	2.0 (1.7)	1.7 (1.0)	t = 1.76; p =.080

Vitamin B_{12}, mean pg/mL (SD)	430.1 (215.8)	427.0 (215.0)	t = 0.11; p =.916
Folic acid, mean ng/mL (SD)	7.7 (4.0)	8.2 (5.0)	t = -1.00; p =.321
Vitamin D_3, mean ng/mL (SD)	32.5 (18.2)	32.1 (12.8)	t = 0.09; p =.929
Malnutrition (%)	25.0	25.7	χ^2 = 0.012; p =1.000
LDL/HDL ratio, mean (SD)	2.1 (0.8)	2.1 (1.0)	t = -0.43; p =.668
Atherogenic coefficient, mean (SD)	2.6 (1.1)	2.6 (1.1)	t = 0.06; p =.955

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; TSH: thyroid-stimulating hormone. *Significant at p<0.05. ***Significant at p<0.001.

According to the CONUT scores, 74.7% of the whole sample showed a normal nutritional status (scores 0-1), 25.3% showed mild malnutrition (scores 2-4) and none moderate or severe malnutrition (scores >4). Differences in blood parameters between patients with malnutrition and well-nourished patients are shown in **Table 3**.

Table 3. Differences in body mass index (BMI) and blood parameters between patients according to their nutritional status. Mean, standard deviation, median and p-value are represented.

	No malnutrition risk (n=208)			Malnutrition risk (n=71)			
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	***p*-value**
BMI (kg/m^2)	26.03	5.25	25.70	25.46	3.97	25.90	0.566
Glucose (mg/dL)	98.48	36.55	90.00	90.51	17.80	88.00	0.155
Creatinine (mg/dL)	0.80	0.25	0.76	0.84	0.32	0.79	0.346
Uric acid (mg/dL)	5.99	1.84	5.80	5.63	1.11	5.60	0.501
Total cholesterol (mg/dL)	186.37	32.07	179.00	125.74	17.30	129.00	<0.01**
LDL cholesterol (mg/dL)	105.59	26.43	102.00	65.10	11.89	66.00	<0.01**
HDL cholesterol (mg/dL)	52.38	16.89	49.00	40.14	8.71	40.00	<0.01**
Triglycerides (mg/dL)	129.16	80.57	112.00	83.55	31.48	77.00	<0.01**
AST (U/L)	25.12	11.93	22.00	31.99	46.14	21.00	0.330
ALT (U/L)	26.46	17.80	21.00	32.09	72.06	19.00	0.453
GGT (U/L)	35.83	44.79	19.50	26.28	46.70	15.50	0.260
Total bilirubin (mg/dL)	0.65	0.86	0.50	0.62	0.29	0.60	0.799
Alkaline phosphatase (U/L)	75.07	26.43	71.00	68.54	30.49	60.00	0.223
Total proteins (g/L)	67.64	5.71	67.00	66.98	6.32	65.00	0.526
Albumin (g/L)	42.44	4.30	42.50	42.02	4.32	42.00	0.571
Prealbumin (g/L)	0.25	0.05	0.25	0.22	0.57	0.21	<0.01**
Sodium (mEq/L)	141.31	3.37	142.00	142.43	2.69	142.00	0.044*
Potassium (mEq/L)	4.29	0.34	4.30	4.25	0.40	4.20	0.440
Calcium (mg/dL)	9.39	0.49	9.30	9.25	0.38	9.20	0.098
Phosphorus (mg/dL)	3.73	0.58	3.70	3.86	0.61	3.80	0.203
Magnesium (mg/dL)	2.14	0.24	2.10	2.09	0.17	2.10	0.257
Zinc (µg/dL)	91.07	17.93	87.00	89.10	15.93	87.00	0.551
Leucocytes (n·10^9/L)	7.38	2.52	7.02	7.02	2.11	6.75	0.398
Haemoglobin (g/L)	139.54	14.55	139.00	140.87	12.85	142.00	0.584
Platelets (n·10^9/L)	244.82	72.50	243.00	238.06	77.21	237.00	0.596
TSH (mUI/L)	1.85	1.23	1.59	1.60	0.88	1.44	0.217
Vitamin B_{12} (pg/mL)	443.73	194.39	383.00	410.11	162.25	388.00	0.309
Folic acid (ng/mL)	8.17	4.83	6.63	6.88	3.24	6.29	0.100
Vitamin D_3 (ng/mL)	32.96	19.05	27.70	31.43	13.71	31.00	0.810

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; TSH: thyroid-stimulating hormone. *Significant at p<0.05. **Significant at p<0.01.

The well-nourished group showed higher mean age (45.6 ± 15.8) compared to the group with malnutrition (37.1 ± 14.8, $p < 0.001$). Women were significantly more likely to have malnutrition (34.7%) compared to men (15.4%, $p = 0.003$).

Patients with cannabis use were more likely to present malnutrition (37.5%) than patients not using cannabis (20.0%, p =0.016), and also patients not taking antidepressants previously to the index admission (28.9% vs 10.8%, p =0.033). In addition, patients who received paliperidone at discharge were more likely to present malnutrition (50.0%) than those not treated with paliperidone at their discharge (20.5%, p =0.002). The rest of treatments received during the hospitalization or at discharge did not reveal significant differences according to the nutritional status.

Nutritional factors associated with malnutrition were total cholesterol, LDL and HDL cholesterol, triglyceride levels, prealbumin and sodium levels (**Table 4**). In the multivariate analysis, none of them showed a predictive potential for malnutrition.

Table 4. Factors associated with malnutrition. Binary logistic regression was performed. Statistical significance was set at p<0.05.

Univariate analysis				
		95%CI		
	OR	LL	UL	Sig (*p*-value)
Age (years)	0.958	0.935	0.982	0.001**
Total cholesterol (mg/dL)	0.797	0.729	0.871	0.000**
LDL colesterol (mg/dL)	0.881	0.834	0.931	0.000**
HDL colesterol (mg/dL)	0.925	0.880	0.971	0.002**
Triglycerides (mg/dL)	0.980	0.969	0.990	0.000**
Albumin (g/L)	0.976	0.900	1.060	0.569
Total proteins (g/L)	0.980	0.923	1.042	0.524
Prealbumin (g/L)	0.000	0.000	0.002	0.000**
Leucocytes (n·10^9/L)	0.939	0.812	1.086	0.396
Sodium (mEq/L)	1.174	1.014	1.360	0.032*
Calcium (mg/dL)	0.511	0.229	1.139	0.100
BMI (kg/m^2)	0.976	0.898	1.060	0.563
LDL/HDL ratio	0.415	0.209	0.821	0.012*
Atherogenic coefficient	0.533	0.318	0.895	0.017*

OR: odds ratio; CI: confidence interval; LL: lower level; UL: upper level; BMI: body mass index. *Significant at p<0.05. **Significant at p<0.01.

3.2.3 Body mass index

Patients were grouped into weight categories using BMI classification as defined by the World Health Organization (WHO) (underweight, BMI <18.50; normal weight, BMI 18.50–24.99; overweight, BMI 25.00–29.99; and obese, BMI ≥30.00) (Khan et al., 2018; WHO,

Considering the whole sample, the percentage of patients with underweight was 2.9%, normal weight 44.0%, overweight 34.9% and obesity 18.2%.

In the subsample of well-nourished patients according to the CONUT score, the percentage of underweight people was 2.9%, normal weight 40.4%, overweight 34.6% and obesity 22.1%. Among patients with a poorer nutritional status, the frequency of underweight was 2.9%, normal weight 41.2%, overweight 47.1% and obesity 8.8%. Differences between groups did not reach statistical significance.

In the group of patients who were not readmitted throughout the follow-up period, the percentage of people with underweight was 4.4%, normal weight 47.4%, overweight 33.3% and obesity 14.8%. Among those who had at least one readmission, the percentage of patients with underweight was 0.0%, normal weight 37.8%, overweight 37.8% and obesity 24.3%, which tended to vary from the other group, without significant differences (p =0.074). However, significant differences were found when mean BMI was compared between readmitted and non-readmitted patients (27.1 ± 5.8 vs 25.3 ± 4.8, p =0.021).

3.2.4 Nutritional status and clinical prognosis

The association between nutritional factors and readmission is represented in **Table 5**. In the multivariate analysis, total cholesterol was associated with higher risk of readmission (p =0.008).

Table 5. Nutritional factors associated with readmission. Binary logistic regression was performed. Statistical significance was set at p<0.05.

	Univariate analysis				Multivariate analysis			
		95%CI				95%CI		
	OR	LL	UL	Sig (*p*-value)	OR	LL	UL	Sig (*p*-value)
BMI (kg/m^2)	1.065	1.008	1.126	0.025*				
Glucose (mg/dL)	0.979	0.964	0.994	0.006**				
Total cholesterol (mg/dL)	1.003	0.995	1.010	0.478	0.015	1.006	1.039	0.008**
LDL colesterol (mg/dL)	1.012	0.999	1.026	0.077				
HDL colesterol (mg/dL)	1.025	0.999	1.052	0.063				
Leucocytes (n·10^9/L)	1.105	1.003	1.217	0.044*				
LDL/HDL ratio	1.102	0.710	1.713	0.665				
Atherogenic coefficient	0.990	0.699	1.401	0.954				

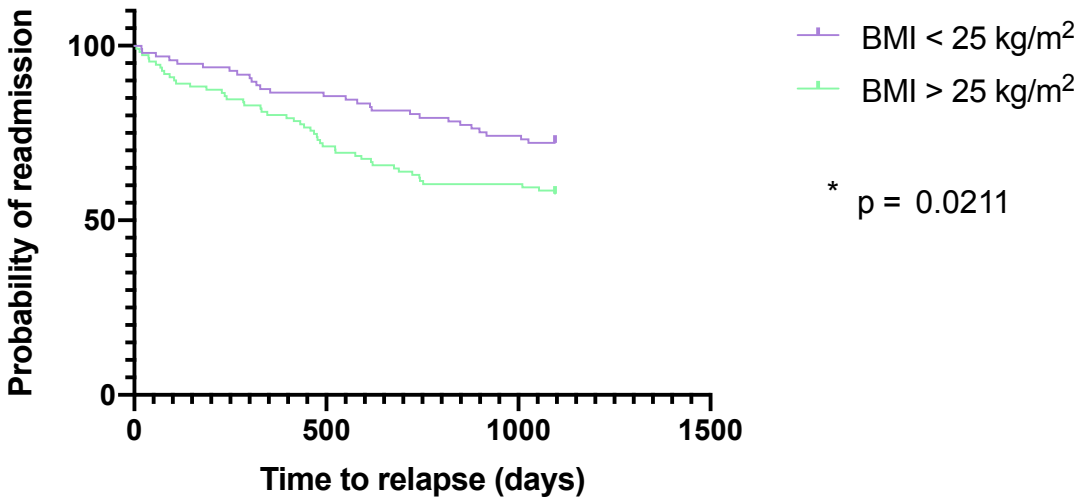
BMI: body mass index; OR: odds ratio; CI: confidence interval; LL: lower level; UL: upper level. *Significant at p<0.05. **Significant at p<0.01.

BMI was negatively correlated with time to relapse (r = -0.162, p =0.019), but not with the number of emergency visits or readmissions during the follow-up period. LDL levels were directly correlated with the number of emergency visits (r = 0.270, p =0.003), the number of readmissions (r = 0.267. p =0.005) and negatively correlated with the time to relapse (r = -0.215, p =0.025). Leucocyte count was also directly correlated with the number of emergency visits (r = 0.162, p =0.007) and readmissions (r = 0.136, p =0.24), and negatively correlated with time to relapse (r = -0.127, p =0.036). Fasting glucose levels were directly correlated with the time to relapse (r = 0.130, p =0.031), and negatively with the number of emergency visits (r = -0.11, p =0.044). LDL/HDL ratio and the atherogenic coefficient were directly correlated with the number of emergency visits (r = 0.230, p =0.015; r = 0.187, p =0.048, respectively), but not with the number of readmissions or with time to the first rehospitalization. The other analytical parameters and the total CONUT score did not show to be correlated with the mentioned prognostic factors.

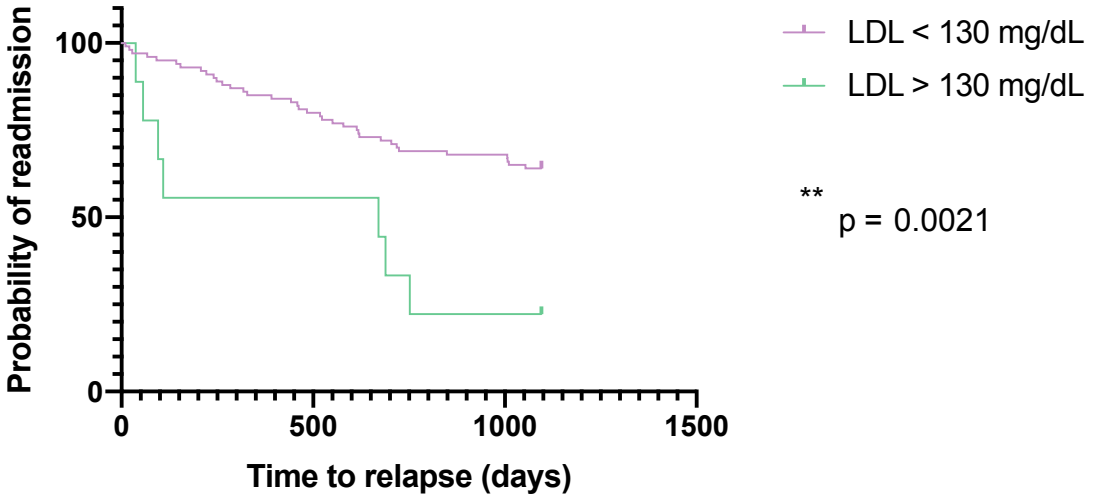
The linear regression analysis showed that LDL cholesterol was associated with the number of admissions in the next three years (odds ratio [OR]: 0.011, 95% confidence interval [95%CI]: 0.003-0.018, p =0.005), and LDL cholesterol and leucocyte count with the number of emergency visits in the next three years (OR: 0.037, 95%CI: 0.013-0.061, p = 0.003; OR: 0.197, 95%CI: 0.054-0.340, p =0.007, respectively). Also, LDL/HDL ratio and the atherogenic coefficient were associated with the number of emergency visits (OR: 1.044, 95%CI: 0.207-1.880, p = 0.015; OR: 0.667, 95%CI: 0.007-1.326, p =0.048, respectively). Finally, LDL cholesterol levels were related to the time until the first readmission (OR: -2.683, 95%CI: [-5.019]-[-0.347], p =0.025), and also BMI (OR: -11.243, 95%CI: [-20.631]-[-1.855], p =0.019), leucocyte count (OR: -18.501, 95%CI: [-35.814]-[-1.188], p =0.036) and fasting glucose (OR: 1.598, 95%CI: 0.151-3.046, p =0.031).

Survival analyses showed a significantly higher event rate in patients with overweight compared to those without overweight (hazard ratio: 0.578, 95%CI: 0.37–0.91, p =0.021), and also in those with LDL levels over 130 mg/dL compared to those with lower blood levels (hazard ratio: 0.302, 95%CI: 0.08–1.12, p =0.002). They also showed a higher probability of readmission in patients with leucocyte count higher than $7.00 \cdot 10^9$/L (hazard ratio: 0.641, 95%CI: 0.43–0.95, p =0.030), and no significant differences between patients with fasting glucose levels higher than 90 mg/dL and those with levels lower than 90 mg/dL (hazard ratio: 1.167, 95%CI: 0.79–1.73, p =0.445) (**Figure 1**).

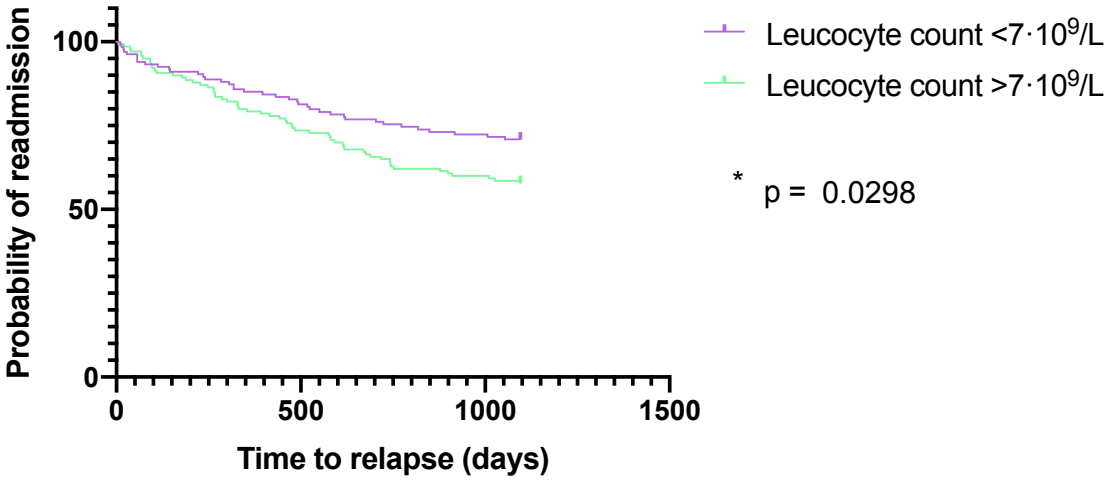
a



b


Probability of readmission
100
50
0
0
500
1000
1500
Time to relapse (days)
LDL < 130 mg/dL
LDL > 130 mg/dL
**
p = 0.0021

c


Probability of readmission
100
50
0
0
500
1000
1500
Time to relapse (days)
Leucocyte count <7·10^9/L
Leucocyte count >7·10^9/L
*
p = 0.0298

d

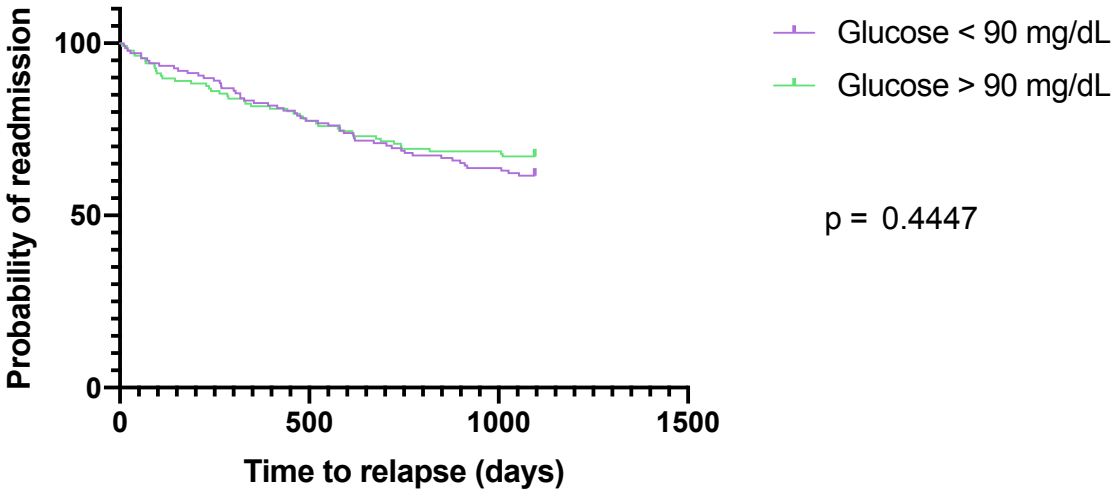

Probability of readmission
100
50
0
0
500
1000
1500
Time to relapse (days)
Glucose < 90 mg/dL
Glucose > 90 mg/dL
p = 0.4447

Figure 1. Probability of readmission and time to relapse in days according to body mass index (BMI) (**1a**), LDL levels (**1b**), leucocyte count (**1c**) and glucose levels (**1d**). Significant differences were found in the survival analysis for BMI (p = 0.021), LDL levels (p = 0.019) and leucocyte count (p = 0.040).

3.2.5 Random Forest prediction of readmission at three years

The model achieved an accuracy of approximately 61.9%, with a sensitivity of 94.0% and a specificity of 14.7%. Variable importance analysis revealed that the ten most crucial predictors influencing the model's performance were: 1) HDL cholesterol, 2) glomerular filtration rate, 3) potassium levels, 4) atherogenic coefficient, 5) phosphorus, 6) alanine aminotransferase (ALT) levels, 7) leucocyte count, 8) vitamin D_3 levels, 9) platelets number, 10) total proteins. These results are represented in **Figure 2**. In the 10-fold cross-validation, the model utilized 500 trees and considered the square root of the predictors at each split. The results of the cross-validation showed that the optimal parameter configuration included a mtry (number of predictors considered at each split) value of 2. This configuration achieved an accuracy of approximately 66.6%, with a Kappa value of 0.0957.

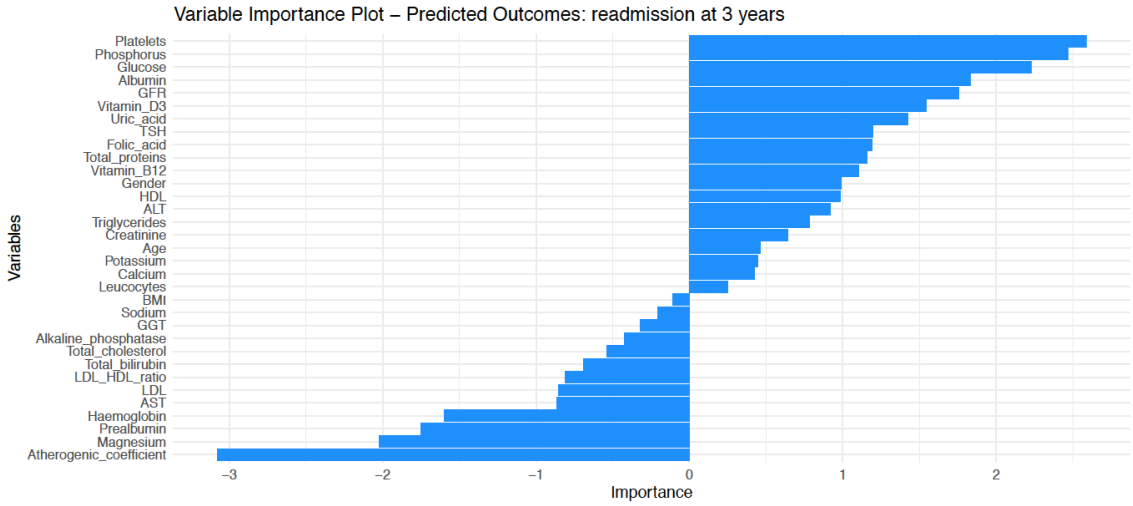


Figure 2. Variable Importance plot with variable importance analysis for predicting readmission at three years. GFR: glomerular filtration rate; TSH: thyroid-stimulating

hormone; ALT: alanine aminotransferase; BMI: body mass index; GGT: gamma-glutamyl transferase; AST: aspartate aminotransferase.

3.2.6 Random Forest prediction of malnutrition

The model achieved an accuracy of approximately 98.2%, with a sensitivity of 100% and a specificity of 92.9%. Variable importance analysis was conducted to identify the key predictors influencing the model's predictions. The top predictors, in order of importance, were HDL cholesterol, glomerular filtration rate, potassium, atherogenic coefficient, phosphorus, ALT, leucocyte count, vitamin D_3 levels, platelets number, and total proteins. These results are shown in **Figure 3**. A 10-fold cross-validation was performed to assess the model's robustness. The optimal configuration involved considering 16 predictors at each split (mtry = 16), resulting in a high accuracy of approximately 98.9%. The Kappa value of 0.9727 indicates strong agreement between the model's predictions and the actual data.

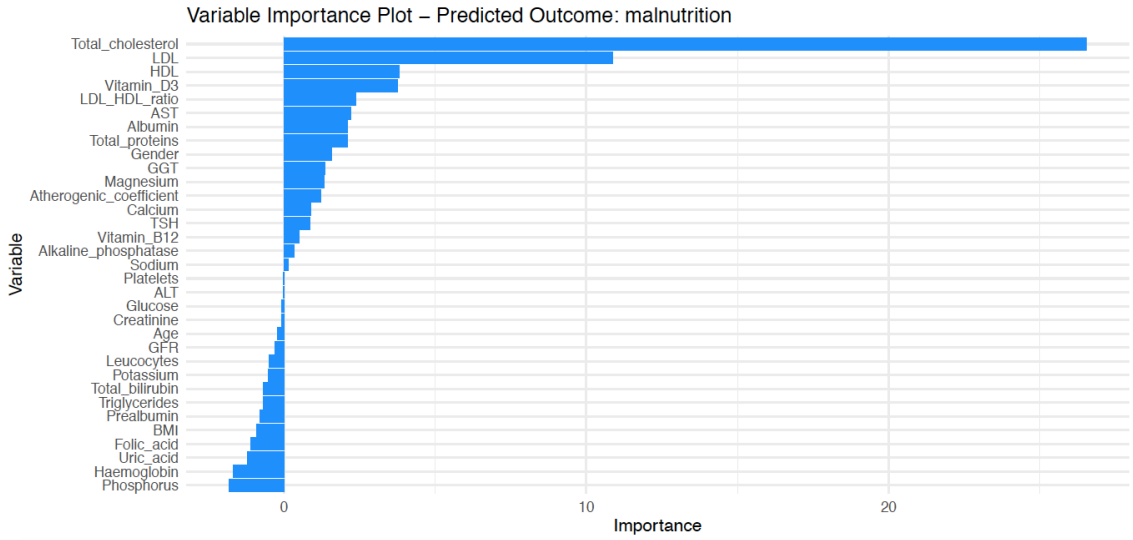


Figure 3. Variable Importance plot with variable importance analysis for predicting malnutrition. AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TSH: thyroid-stimulating hormone; ALT: alanine aminotransferase; GFR: glomerular filtration rate; BMI: body mass index.

Discussion

Previous evidence has reported the impact of psychiatric illnesses, including BD, and pharmacological treatments used for their treatment on somatic comorbidity (331). In turn, somatic conditions, such as impaired glucose metabolism, have been associated with a worsened psychiatric prognosis (111). Some studies have described the nutritional status of patients with eating disorders (332–334), and others have identified nutritional factors that can influence the course of acute psychiatric admissions (318).

The literature shows that patients with BD have higher mean BMI, waist circumference, and non-HDL cholesterol levels compared to healthy controls (304–306), and higher BMI has been associated with higher inflammatory levels, higher prevalence of suicide attempts, medical comorbidities and more severity of the psychiatric illness (323).

The present work shows through a longitudinal study that 36.2% of patients admitted with a manic episode were readmitted to a psychiatric hospitalization unit in the following three years, and 25.3% of the whole sample presented a poor nutritional status according to the CONUT score. Considering the correlation of CONUT scores with a worse clinical prognosis in somatic disorders (78,335), this study aimed to evaluate the association of malnutrition with the course of illness in the following three years. Our results suggest that the nutritional status measured with the CONUT score might not be a feasible predictor for clinical prognosis in BD, but specific independent factors, especially total cholesterol, as shown in the multivariate analysis, might be associated with psychiatric readmissions. Leucocyte count, BMI and LDL cholesterol levels were associated with a higher number of readmissions and correlated with a shorter time to relapse requiring readmission. In addition, higher LDL cholesterol levels and leucocyte count were correlated with a higher number of emergency visits during the follow-up period. When metabolic and nutritional parameters were compared between readmitted and non-readmitted patients, lower fasting glucose levels, higher leucocyte count, higher BMI, and higher total cholesterol levels were found in the first group.

Thus, a poorer nutritional status might not reflect the severity of the illness in patients with BD, but specific parameters might be used in future long-term prospective studies

in order to confirm their association with a worse prognosis, and also to determine if those parameters associated with a poorer short-term prognosis should be considered also risk factors also for an adverse course of illness in the long term.

Other interesting results derived from this study reflect a higher likelihood of presenting malnutrition in those patients using cannabis, patients not taking antidepressants previously to the index admission, and those receiving paliperidone at discharge. From a nutritional point of view, parameters associated with malnutrition were lower total cholesterol, LDL and HDL cholesterol levels, lower triglyceride and prealbumin levels, and higher sodium levels. The random forest model results supported the findings associating different factors from the lipid profile as potential predictors of malnutrition.

Special attention should be paid to patients with determined clinical and nutritional characteristics in order to identify those at higher risk for presenting a poorer nutritional status. This subgroup of patients might present reduced food intake or a higher tendency to poorer self-care, but future studies should be conducted in order to confirm this hypothesis and help clinicians develop adequate nutritional risk screening tools (336–338) in order to identify and develop specific interventions (339,340).

Previous studies have found a significant proportion of patients with mental illnesses with overweight, which could be due to different factors, such as lifestyle and habits, pharmacological treatments, and mental illnesses themselves. Contrary to previous evidence aimed at determining nutritional deficiencies in patients with mental illnesses (318), our study did not find an association between BMI and risk of malnutrition.

Regarding the machine learning predictive algorithms, while the model predicting rehospitalization at three years excels in correctly identifying patients requiring hospital admission (high sensitivity), it struggles with specificity, leading to a relatively high rate of false positives. The prediction of rehospitalization might be influenced by more factors, including social support, and severity of the diagnosis, and the predictive algorithm might require an integration of more clinical variables for its enhancement in real-world practice. On the other side, our RF model exhibited outstanding performance in predicting malnutrition, with high accuracy, sensitivity, and specificity. The identified key predictors, most of them from the lipid profile, shed light on the underlying factors

contributing to malnutrition risk. This model's proficiency and robustness, as demonstrated through cross-validation, make it a promising tool for identifying patients at risk of malnutrition, facilitating timely interventions, and improving patient outcomes.

Considering the findings reported, we recommend to conduct a global assessment of the nutritional and metabolic status of patients with BD admitted to an acute psychiatric unit, and consider them as factors that might influence both the organic and mental well-being of these individuals. We also suggest including periodical assessments during their follow-up at the outpatient unit. These preventive evaluations might allow the identification of subpopulations in which psychosocial and lifestyle interventions should be prioritized (339), in order to empower patients at higher risk for a poorer nutritional status to maintain healthy routines, which could lead to an improvement of their somatic and psychiatric prognosis and their quality of life. Psychoeducation on BD should also be considered in subgroups at higher risk of psychiatric relapse in order to identify prodromic symptoms, promote healthy habits, and thus reduce the risk of presenting new episodes and requiring readmission (341).

Given that periodical blood tests and anthropometric measures are performed in outpatient units periodically, our findings aim to encourage the increase of the available evidence regarding the influence of metabolic and nutritional parameters in the course of BD. Novel findings might serve clinicians for the identification of target populations in whom medical and psychiatric prognosis might be enhanced. Further studies will also elucidate the influence of pharmacological treatment, diet and other environmental factors on patients' nutritional status. Also, future evidence could increase the knowledge regarding the relationship of specific blood and metabolic parameters with prognostic factors related to psychiatric illness, such as frequency of clinical relapses, number of admissions, and suicidal behaviour.

This study comes with some strengths and limitations. Even though metabolic parameters have been previously correlated with psychiatric prognosis in BD (111), to the authors' knowledge, there is a gap in the literature regarding the relationship between the global nutritional status of psychiatric inpatients and the illness' prognosis, and this article aims to provide some evidence in this issue using a longitudinal design. In addition, the description of the nutritional status in patients with BD might help determine the

influence of pharmacological treatments, lifestyle habits and diet on somatic health, and might allow the implementation of individualized interventions in determined profiles. In our study, the use of the CONUT score, an objective and validated screening tool, and also the use of machine learning algorithms, confer higher reliability to the results obtained. The limitations of this study include the follow-up period, limited to three years after the index admission, and the lack of other prognostic factors, such as the presence of suicide attempts or the total number of relapses, including those not requiring an acute admission. Another limitation is the observational nature of the follow-up, which enhances generalizability but may include confounders such as medication (342).

However, this longitudinal study is a first approach to study the influence of nutritional and metabolic factors on the course of illness in BD that aims to promote the development of future studies, which may help identify parameters that might predict treatment response or psychiatric prognosis and demonstrate the beneficial effects of preventive nutritional and lifestyle therapeutic interventions in patients with BD.

Conclusion

Our results showed a lack of association between malnutrition, defined as a CONUT total score between 2 and 12, and higher risk of readmission. However, lower fasting glucose levels, higher leucocyte count, higher BMI and higher total cholesterol levels were found in patients who were readmitted during the following three years after an admission with a manic episode. A significant association was found between higher total cholesterol levels with higher number of readmissions, and higher BMI, LDL levels and leucocyte count with a shorter time to relapse requiring readmission. Higher LDL levels and leucocyte count, higher LDL/HDL ratio and atherogenic coefficient were also correlated with higher number of emergency visits during the three-year follow-up period. The machine learning algorithm used showed a strong potential of nutritional variables to predict malnutrition, which was lower for predicting readmission at three years. Our results suggest that specific nutritional parameters, but not malnutrition, might be associated with the course of psychiatric admissions, which might allow the identification

of specific patients' profiles in which lifestyle interventions might be promoted with a special focus.

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5. DISCUSSION

5.1. Discussion of the findings

Previous evidence has shown that individuals with severe mental illnesses have on average unhealthier lifestyles, less physical activity, and poor dietary habits compared to the general population. These factors, added to the use of pharmacological treatments and the psychiatric illnesses by themselves, increase the risk of a poor nutritional status, which is often masked by patients' overweight status, and metabolic comorbidities (60). Besides, it is known that somatic conditions, and especially metabolic comorbidities, may have an impact on the course of the psychiatric illnesses (111). However, limited data are available regarding nutritional status in severe mental disorders, such as BD, and its impact on the illness course, added to the lack of malnutrition risk screening tools proposed in this population (317,333,334).

The present work shows through a cross-sectional study a considerable rate of individuals at risk of malnutrition (defined by CONUT score ≥ 2) in a sample of patients admitted in an acute psychiatric unit (42.5%), which is consistent with other studies using the same nutritional screening tool (343,344). Considering that previous evidence has correlated CONUT scores with a worse clinical prognosis in populations with somatic disorders, including longer hospitalizations (78), this study aimed to evaluate the association of nutritional parameters with the length of stay and also to find specific parameters that might better predict the nutritional global status of inpatients.

Our results did not reveal a significant association between risk of malnutrition and length of stay when nutritional status was assessed with the CONUT score. However, plasmatic protein levels, transferrin saturation and iron levels showed a significant inverse correlation with the days of hospitalization, indicating a potential effect of nutritional parameters on the course of acute psychiatric admissions. These results suggest that, although specific nutritional parameters seem to be related to greater length of stay, the CONUT score might not be the best short-term predictor in psychiatric hospitalizations. This could be associated with the fact that, in an acute psychiatric ward, behavioral abnormalities and psychopathology are treated in an individualized manner, with some patients with severe episodes being treated with higher doses of the indicated treatment

or with specific drugs aimed at compensating acute episodes. Thus, the length of stay might not be reflecting the severity of psychiatric conditions in all cases.

In the same study, the correlation of specific nutritional parameters with nutritional status was assessed. Apart from the parameters included in the CONUT screening tool, low zinc, iron, total proteins, prealbumin, transferrin, triglyceride levels, a low transferrin saturation index, and BMI, were indicators of a poorer nutritional status, since they were correlated with the CONUT total score. In addition, most parameters were correlated between them. The subgroup of patients with lower BMI and risk of malnutrition might present reduced food intake or higher tendency to a poorer self-care, but further evidence is needed to confirm this hypothesis. However, a significant proportion of patients at risk of malnutrition were overweighted, which can be due to several factors, such as lifestyle and habits, pharmacological treatments and mental illnesses by themselves.

Our results demonstrate a strong association between several analytical parameters and allow the identification of specific subgroups, such as those with greater alteration of nutritional parameters, that may present longer courses of illness, having also demonstrated in previous evidence worse medical prognosis (78). Even though an important correlation between different nutritional parameters was found and all of them were correlated with risk of malnutrition, this study identified cholesterol levels, lymphocyte count, zinc levels, and BMI as independent factors associated with an increased risk of malnutrition, which underscores the importance of their assessment in clinical practice.

The presence of BD or other psychiatric diagnoses and the pharmacological treatment received did not seem to have influence over nutritional status or days of hospitalization. Moreover, the diagnosis of BD, other psychiatric diagnoses or specific psychotropic drugs did not seem to increase the risk for malnutrition or for a worse course of acute psychiatric admissions, basing the associated findings on analytical parameters. However, in 13.8% of the patients, obesity with nutritional deficiency according to CONUT score was found, which emphasizes the importance to characterize the different nutritional profiles of these individuals according to their nutritional status (345,346). The identification of specific phenotypes might allow clinicians to develop adequate nutritional risk screening tools considering specificity of the psychiatric population (336,337), and also to design determined approaches for different clinical situations (339,340).

According to our findings, a global assessment of the nutritional status through the study of different analytical parameters and BMI should be considered in all cases during acute psychiatric hospitalizations, since these factors might influence the organic and mental well-being of patients. The authors also recommend a periodical study of patients' nutritional status from the outpatient unit and not only in case of acute hospitalization, since this might allow the identification of determined subgroups that could benefit from psychosocial and lifestyle interventions, the prescription of nutritional supplementation in specific cases (339), as well as the implementation of individual or group sessions aimed to the assessment of daily habits and the promotion of healthy routines. These strategies might provide patients some skills that lead to an improvement of their nutritional status, their medical and psychiatric prognosis and their quality of life. Special attention should be paid to those patients with poor social support and severe mental illnesses in order to detect and manage a potential malnutrition status.

Acute psychiatric admissions should serve as an opportunity for clinicians to identify existing abnormalities, since a poor nutritional status has been correlated with higher rates of adverse prognostic factors (78). According to our results, altered levels of cholesterol, lymphocyte count, zinc, and low BMI should be considered as potential indicators of a poor nutritional status. Given the gap in the literature with regard to the nutritional status in psychiatric populations, its description in these individuals, including anthropometric measurements, functional evaluation, dietary habits, and medical history, might help determine the influence of pharmacological treatments, lifestyle habits, and the different psychiatric illnesses on somatic health, and to identify those patients at increased risk of malnutrition. Patients with insufficient levels of different nutritional parameters might be a target for nutritional and lifestyle interventions aimed to improve their physical and mental health.

Previous evidence has reported the impact of psychiatric illnesses, including BD, and pharmacological treatments used for their treatment on somatic comorbidity (331), and somatic conditions have been associated with a worsened psychiatric prognosis (111). The literature shows that patients with BD have higher mean BMI, waist circumference, and non-HDL cholesterol levels compared to healthy controls (304–306), and higher BMI has been associated with higher inflammatory levels, higher prevalence of suicide attempts, medical comorbidities and more severity of the psychiatric illness (323).

Considering our previous findings and the scarcity of prospective designs in the literature, a different study was performed aimed at determining longitudinally the effects of the nutritional status in the course of the psychiatric illness in the following three years, focusing on patients with BD admitted to our acute psychiatric ward with a manic episode. We found that 36.2% of patients admitted with a manic episode were readmitted to a psychiatric hospitalization unit in the first three years, and 25.3% of the whole sample were at risk for a poor nutritional status according to the CONUT score. The nutritional status measured with the CONUT score was not found as a feasible predictor for clinical prognosis in BD. However, specific independent factors, especially total cholesterol, as shown in the multivariate analysis, were associated with psychiatric readmissions. Higher leucocyte count, BMI and LDL cholesterol levels were associated with a higher number of readmissions and correlated with a shorter time to relapse requiring readmission. Moreover, higher LDL cholesterol levels and leucocyte count were correlated with a higher number of emergency visits during the follow-up period. When the parameters assessed were compared between readmitted and non-readmitted patients, lower fasting glucose levels, higher leucocyte count, higher BMI, and higher total cholesterol levels were found in the first group. Thus, a poorer nutritional status might not reflect the severity of the illness in patients with BD, but determined parameters might be used in future long-term prospective studies to confirm their association with a worse prognosis, and also to assess whether those parameters associated with a poorer short-term prognosis should be considered risk factors for an adverse course of illness in the long term.

This study identified specific patients' profiles associated with a higher likelihood of being at risk of malnutrition, such as cannabis use, not taking antidepressants previously to the index admission, and receiving paliperidone at discharge. From a nutritional point of view, parameters associated with an increased risk of malnutrition were lower total cholesterol, LDL and HDL cholesterol levels, lower triglyceride and prealbumin levels, and higher sodium levels. The random forest model results supported the findings associating different factors from the lipid profile as potential predictors of malnutrition.

Thus, special attention should be paid to patients with determined clinical and analytical characteristics to identify those at higher risk for presenting a poorer nutritional status and worse psychiatric outcomes in the future. Future studies should be conducted in

order to confirm this hypothesis and help clinicians develop adequate nutritional risk screening tools (336–338) to identify and develop specific interventions (339,340).

Despite previous evidence showing a significant proportion of patients with mental illnesses and overweight, in this study we did not find an association between BMI and the risk of malnutrition.

Regarding the machine learning predictive algorithms used, while the model predicting rehospitalization at three years showed high sensitivity in correctly identifying patients requiring hospital admission, it struggled with specificity, leading to a relatively high rate of false positives. The prediction of readmission might be influenced by more factors, including social support, and severity of the diagnosis, among others, and the predictive algorithm might require an integration of more clinical variables for its enhancement in real-world practice. On the other side, our RF model exhibited outstanding performance in predicting malnutrition, with high accuracy, sensitivity, and specificity. The identified key predictors, most of them from the lipid profile, shed light on the underlying factors contributing to malnutrition risk. This model's proficiency and robustness, as demonstrated through cross-validation, make it a promising tool for identifying patients at risk of malnutrition, which could facilitate timely intervention and improve patient outcomes.

Considering the findings reported in this study, a global assessment of the nutritional and metabolic status of patients with BD admitted to an acute psychiatric unit, and also periodically during the follow-up, might allow their consideration as potential factors that might influence both the organic and mental well-being of patients, and the identification of subpopulations in which psychosocial and lifestyle interventions should be prioritized (339), in order to empower patients at higher risk for a poorer nutritional status to maintain healthy routines, improve their somatic and psychiatric prognosis and their quality of life. Psychoeducation on BD should also be considered in subgroups at higher risk of psychiatric relapse in order to identify prodromic symptoms, promote healthy habits, and thus reduce the risk of presenting future relapses and readmissions (341).

A proper nutritional status allows the maintenance of metabolic functions, whereas impaired nutritional and metabolic parameters may influence energy availability, promote oxidative stress and alter other cellular functions. However, BD has been postulated as

a biphasic disorder of energy availability, with increased energy production in mania and reduced in depression, which suggests that different mood states might be associated with variations in mitochondrial function despite maintaining similar nutrient supplies within the same individuals, and that mitochondrial dysfunction could serve as a state-dependent marker of this psychiatric illness. However, genetic predisposition, the nutritional status and metabolic factors, among others, are responsible for a high inter-individual variability in cellular functions, and specifically in mitochondrial function, which impairs the assessment of metabolic variations between different acute mood states in BD. Thus, this work aimed at assessing potential intraindividual variations in metabolic functions in BD during acute mood episodes by the assessment of bioenergetic functions, and specifically mitochondrial ETC respiratory capacity.

The results derived from this work highlight that mitochondrial function might be altered during mood states in BD (both mania and depression), which might revert after clinical remission, and that potential biomarkers that could be identified during manic or depressive phases might not be found in euthymia. Thus, in line with previous hypotheses, these results suggest that mitochondrial respiratory capacity could be a biomarker of illness activity and clinical response in BD.

Globally, our longitudinal results showed lower maximal ETC oxygen consumption capacity in acute episodes of BD compared with euthymia after boosting mitochondrial respiration in living PBMC. Interestingly, the overall patients' cohort showed a significant improvement in mitochondrial respiratory capacity from the acute phase to euthymia, with a greater tendency in the manic group compared to the depressive sample. However, the statistical power might have been influenced by the limited sample size, especially in the depressive subsample. The significant results obtained were not influenced by the smoking status. These results might evidence an ETC dysfunction and thus an impaired aerobic respiration in both manic and depressive episodes of BD, which could be a risk factor for an increased anaerobic respiration and also oxidative stress. The results also reveal a potential relationship between energy and activity items with maximum mitochondrial respiratory capacity; however, these data should be interpreted with caution given the limited sample size included. Further studies should elucidate whether, as observed in our sample, late insomnia is associated with enhanced mitochondrial respiratory capacity. Despite this study suggests that pharmacological treatment might not influence mitochondrial function, some previous evidence has

reported an impact of different drugs, especially antipsychotics, in mitochondrial activity (347,348), which should also be addressed in future studies with larger cohorts.

In this study, patients and healthy controls were assessed in the same conditions regarding fasting status, time of the day, sample processing and experimental procedures performed in order to ensure the comparability of the results obtained. Comparisons between acute phases and healthy controls revealed significant differences in ETC rates, mainly due to a reduced maximum OCR in bipolar depression compared to the other groups. Previous studies have similarly reported reduced mitochondrial respiratory capacity in major depressive disorder (349). However, considering inter-individual variability in mitochondrial function, our results may be interpreted as an improvement in mitochondrial respiratory capacity after achieving symptomatic remission, which should be explained by a potentially normalized mitochondrial function in clinical stability if it is confirmed in future analyses.

Previous research supports the presence of mitochondrial dysfunction in patients with BD. Nevertheless, to the authors' knowledge, this is the first study reporting intra-subject longitudinal differences between acute mood episodes and clinical remission. In addition, this study examines in vivo PBMC oxygen consumption capacity right after blood extraction and processing. Other studies assessing mitochondrial OCRs in mood disorders have been conducted with smaller samples (350,351).

In addition, the available evidence in the literature comparing mitochondrial function between patients with BD and healthy controls is limited, and mitochondrial function in BD is often assessed in the absence of an acute mood episode at the moment of study, with a lack of studies comparing intra-subject differences and an important variety of methods used to assess mitochondrial function. This is added to the fact that, in BD patients, *in vivo* mitochondrial respiratory capacity has been assessed in smaller cohorts.

Preliminary findings from the subsample of patients in whom aerobic capacity was also assessed revealed no significant differences in endurance time, VO_2peak or oxygen consumption at the anaerobic threshold during CWRCE between severe acute mood states and after clinical remission, despite mitochondrial respiration showed a tendency to increase in clinical remission compared to the acute states. An inverse association was found between basal oxygen consumption and maximum mitochondrial respiratory capacity after clinical remission, suggesting individuals with increased mitochondrial

capacity might have lower basal oxygen requirements and higher mitochondrial efficiency, which should be confirmed in larger samples. The maximum oxygen uptake during the effort test after clinical remission was inversely correlated with basal mitochondrial respiration, indicating that physical fitter individuals may exhibit lower resting mitochondrial oxygen requirements. Our results suggest an association between mitochondrial ETC dysfunction and an impaired aerobic respiration, which could be a risk factor for an increased anaerobic respiration and oxidative stress.

In addition, higher BMI tended to be correlated with longer endurance time after clinical remission, hinting a better physical fitness in this cohort. Also, IPAQ total score was associated with more prolonged endurance time during the acute state, revealing a stronger association of endurance capacity with physical fitness rather than with the severity of the acute episode.

To the authors' knowledge, no studies have reported previously intra-subject longitudinal differences in BD between acute states and clinical remission or have assessed the potential association between oxygen consumption capacity during an effort test and mitochondrial respiration. Thus, these preliminary results aim to shed light on this field and motivate future research in larger cohorts, in which, given the number of variables influencing bioenergetic functions, such as physical fitness, lifestyle habits, the nutritional status, and genetic predisposition, among others, might contribute through longitudinal studies focused on the assessment of intra-individual differences to the understanding of the underlying pathophysiological mechanisms in BD, and to the identification of specific biomarkers associated with the severity and the course of this illness.

5.2. Limitations

With regard to the assessment of the global nutritional status of psychiatric inpatients, its cross-sectional design cannot reveal causal dynamics between the variables included, and cannot allow the inclusion of other nutritional factors that were not obtained during the admission. However, this cross-sectional study can represent a picture of the nutritional status of acute psychiatric inpatients and is a first approach to study the interaction between specific factors related with their disease and malnutrition, which may in the future open new opportunities for individualized interventions.

To progress in this field, a longitudinal study was conducted in patients admitted with a manic episode to assess the impact of nutritional factors on the course of the illness in the following three years. In this study, the use of the CONUT score, an objective and validated tool, and also the use of machine learning algorithms, confer higher reliability to the results obtained. However, different limitations were identified, such as the follow-up period, limited to three years after the index admission, and the lack of other prognostic factors, such as the presence of suicide attempts or the total number of relapses, including those not requiring an acute admission. Another limitation is the observational nature of the follow-up, which enhances generalizability but may include confounders such as medication (342). However, this longitudinal study is a first approach to study the influence of nutritional and metabolic factors on the course of illness in BD that aims to promote the development of future studies, which can overcome the identified limitations and may help identify parameters to predict treatment response or psychiatric prognosis and demonstrate the beneficial effects of preventive nutritional and lifestyle therapeutic interventions.

Considering the sample recruited for the assessment of mitochondrial respiratory capacity, a major strength is the cohort, longitudinal design, which, however, is one of the reasons for the first limitation, the small sample size. Moreover, this patients' profile included in the study, a short course of disease during high severity acute mood episode requiring admission to an acute psychiatric unit, also limited the sample size. However, compared to previous studies, the sample obtained was larger, and the study design allowed to perform intra-individual comparisons between two highly different clinical states. The novel method of obtaining *in vivo* ETC oxygen consumption capacity with a respirometer differs from most previous evidence that used different methods to address the study of mitochondrial function. This method allows to assess mitochondrial respiration in fresh, right after the blood extraction, and then requires a link between the inpatient unit and a specialized laboratory. Laboratory measurements were performed at the same time as the clinical evaluation, since the experiment used requires the assessment of ETC respiratory capacity from living cells right after the blood centrifugation procedure. However, the specific method used limits comparability with previous studies assessing mitochondrial dysfunction with different tools. Also, the results obtained in this study were not contrasted with different analyses aimed to measure mitochondrial function in patients with BD. This hinders the capacity to reach a conclusion regarding the presence of mitochondrial dysfunction in patients during an

acute phase, which should be addressed with further specific analyses. Even though the inpatient unit ensures a lower variability in different environmental conditions, since illicit substances and tobacco are strictly forbidden, caffeine consumption is not allowed and a balanced diet is provided in all cases, other factors might influence ETC respiration. Some of these include pharmacological treatments, especially antipsychotics, which are commonly used in mania, have significant effects on mitochondrial functioning and generally suppress mitochondrial biogenesis (352,353). Some of these variables (i.e., age, sex) were controlled for. On the other hand, the possibility of obtaining our results at two different times in the same patients during their admission in the acute psychiatric unit allows to reduce potential confusion factors.

The subsample in which the aerobic capacity was assessed apart from mitochondrial respiratory capacity also allows intra-individual comparisons between different clinical states in patients with short course of illness and severe mood episodes. Also, laboratory measurements were performed at the same time as the clinical evaluation and the effort tests in the cycle ergometer were obtained. However, the small sample size is the main limitation of this study, explained by the severity of mood episodes, which hindered recruitment. The limited sample size did not allow differentiation from participants at index mania and index depression, which might be expected to differ. In addition, healthy controls were not included in this study. Finally, even though the inpatient unit ensures a lower variability in different environmental conditions, a variety of factors, such as some individual characteristics, might have influenced aerobic capacity.

5.3. Future research lines

Based on the reported findings, further studies using prospective models should be conducted to evaluate useful nutritional screening and assessment tools and identify those mostly associated with different course of the psychiatric illnesses in the long term. Also, future evidence should elucidate if the nutritional parameters associated with a poorer short-term prognosis could be considered risk factors also for an adverse course of illness. The results obtained from this work aim to drive a line of research in which nutritional and metabolic data may serve clinicians for wider interventions beyond the improvement of the psychiatric episodes and medical comorbidities. Since periodical blood tests and anthropometric measures are performed in outpatient units, the design of new studies targeting nutritional and metabolic parameters in psychiatric patients

might be also useful to distinguish in the future profile of patients who are at higher risk for either suffering medical comorbidities or presenting with adverse circumstances related to their psychiatric disorder. Further studies will also elucidate the influence of pharmacological treatment, diet and other environmental factors on patients' nutritional status. Upcoming evidence could increase the knowledge regarding the relationship of specific blood and metabolic parameters with prognostic factors related to psychiatric illness, such as frequency of clinical relapses, number of admissions, and suicidal behaviour. Novel findings might serve clinicians for the identification of target populations in whom medical and psychiatric prognosis might be enhanced.

In addition, future studies might link the impact of metabolic and nutritional impairments, including malnutrition and MetS, on cellular metabolic functions, such as mitochondrial function, during different mood states in BD. Longitudinal studies with larger samples, including medication-free participants, would be useful in the study of mitochondrial dysfunction in BD, contribute to the correlation of different mitochondrial dysfunction parameters and identify state-dependent biomarkers that may in the future open new opportunities for individualized interventions aimed to enhance mitochondrial function. Future studies on mitochondrial function should also consider its assessment from brain-derived exosomes and study the correlation between brain and peripheric mitochondrial activity. The correlation between mitochondrial dysfunction in patients with BD and the severity of cognitive impairments, though the use of neuroimaging and neuropsychological assessments, should also be addressed in the future.

The relationship between impaired mitochondrial function and patients' characteristics, including disease severity, clinical features, lifestyle habits and nutritional parameters, should be addressed in future studies. Different markers of mitochondrial function and oxidative stress should also be studied to identify potential phase-specific biomarkers. For instance, transcriptomic analyses, enzymatic activities of the mitochondrial ETC, plasmatic mtDNA content, inflammatory parameters and oxidative stress parameters, such as lactate, pH, uric acid, glucose, and ROS, could potentially be useful to increase the knowledge around the role of mitochondrial function in BD, allow the identification of specific biomarkers in acute mood states and the design of specific interventions in the treatment of acute episodes or in relapse prevention in BD. Mitochondrial-related biomarkers, together with nutritional and metabolic factors, neuroimaging and neuropsychological studies, should be assessed to identify specific patients' profiles and

elucidate their impact in BD prognosis. In addition, future studies should address the potential impact of the endocannabinoid system and other pathways associated with mitochondrial function in individuals with BD.

Lastly, further studies should elucidate whether aerobic exercise could enhance mitochondrial respiratory capacity, whether this could be used as a state-dependent marker in the assessment of clinical response, and if the enhancement of physical activity and specific dietary patterns might be potential strategies to prevent not only metabolic comorbidities, but also mitochondrial dysfunction, relapses and cognitive impairments in BD.

The determination of specific biomarkers might allow the identification of different clinical phenotypes and guide towards the design of future interventional studies targeting mitochondrial function at specific levels, which might modify the course of disease and pave the way for personalized interventions in BD.

6. CONCLUSIONS

1. The cumulative findings highlight various nutritional and bioenergetic parameters that may be related with the course of illness in individuals with bipolar disorder.
2. Among patients admitted to an acute psychiatric ward, plasmatic protein levels, transferrin saturation and iron levels are inversely correlated with length of stay.
3. In acute psychiatric hospitalizations, the nutritional status is reflected by cholesterol, albumin, lymphocyte count, zinc, iron, prealbumin, transferrin, triglycerides, transferrin saturation, and body mass index.
4. While the determination of high risk of malnutrition according to the *Controlling Nutritional Status* total score may have limited effectiveness in robustly predicting the course of bipolar disorder, specific parameters, including lower fasting glucose levels, higher leucocyte count, higher body mass index and higher total cholesterol levels might be associated with psychiatric readmissions during the following three years after an admission with a manic episode.
5. Higher total cholesterol levels have been associated with higher number of readmissions, and higher body mass index, LDL levels and leucocyte count with a shorter time to relapse requiring readmission. The augmentation of clinical variables with additional factors, such as biomarkers (e.g., mitochondrial function, genetics), could enhance the predictive accuracy of outcomes in bipolar disorder.
6. Mitochondrial oxygen consumption capacity emerges as a potential state-dependent biomarker in individuals with bipolar disorder, with reduced maximum mitochondrial respiratory capacity found in patients with an acute episode of bipolar disorder compared to clinical remission.
7. Bipolar depression might be associated with lower levels of mitochondrial respiratory capacity compared to mania, and manic episodes with a higher tendency to restore respiratory capacity at clinical remission compared to depressive episodes.
8. Impaired mitochondrial oxygen consumption capacity might be reflected by exercise performance, and physical fitness might predict a better exercise performance over the illness' state, indicating the influence of different personal factors in bioenergetic functions, which underscores the relevance of assessing intra-individual differences in the study of state-dependent biomarkers in bipolar disorder.

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