Importance of immunometabolic markers for the classification of patients with major depressive disorder using machine learning

Yolanda Sánchez-Carro [a,b,c], Alejandro de la Torre-Luque [c,d], Itziar Leal-Leturia [a,b,c],
Neus Salvat-Pujol [e,f], Clara Massaneda [e], Aida de Arriba-Arnau [e], Mikel Urretavizcaya [c,e,g],
Victor Pérez-Solà [c,h,i], Alba Toll [i], Antonio Martínez-Ruiz [j], Raquel Ferreirós-Martínez [k],
Salvador Pérez [l], Juan Sastre [l], Pilar Álvarez [m], Virginia Soria [c,e,g], Pilar López-García [a,b,c,*]

[a] Department of Psychiatry, Universidad Autonoma de Madrid (UAM), Spain
[b] Department of Psychiatry, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain
[c] Center for Biomedical Research in Mental Health (CIBERSAM), Carlos III Health Institute, Madrid, Spain
[d] Department of Legal Medicine, Psychiatry and Pathology, Universidad Complutense de Madrid, Spain
[e] Bellvitge University Hospital, Department of Psychiatry, Bellvitge Biomedical Research Institute (IDIBELL), Neurosciences Group - Psychiatry and Mental Health, Barcelona, Spain
[f] Corporació Sanitària Parc Taulí, Department of Mental Health, Sabadell, Spain
[g] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona (UB), Spain
[h] Universitat Pompeu Fabra (UPF), Barcelona, Spain.
[i] Psychiatry Department, Institut de Neuropsiquiatria i Addicions, Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[j] Unidad de Investigación, Hospital Universitario Santa Cristina, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain.
[k] Service of Clinical Analysis, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain
[l] Department of Physiology, Faculty of Pharmacy, University of Valencia, Spain
[m] Psychiatry Department, Institut de Neuropsiquiatria i Addicions, Centre Fòrum, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

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ABSTRACT

Background: Although there is scientific evidence of the presence of immunometabolic alterations in major depression, not all patients present them. Recent studies point to the association between an inflammatory phenotype and certain clinical symptoms in patients with depression.

The objective of our study was to classify major depression disorder patients using supervised learning algorithms or machine learning, based on immunometabolic and oxidative stress biomarkers and lifestyle habits.

Methods: Taking into account a series of inflammatory and oxidative stress biomarkers (C-reactive protein (CRP), tumor necrosis factor (TNF), 4-hydroxynonenal (HNE) and glutathione), metabolic risk markers (blood pressure, waist circumference and glucose, triglyceride and cholesterol levels) and lifestyle habits of the participants (physical activity, smoking and alcohol consumption), a study was carried out using machine learning in a sample of 171 participants, 91 patients with depression (71.42% women, mean age = 50.64) and 80 healthy subjects (67.50% women, mean age = 49.12).

The algorithm used was the support vector machine, performing cross validation, by which the subdivision of the sample in training (70%) and test (30%) was carried out in order to estimate the precision of the model.

The prediction of belonging to the patient group (MDD patients versus control subjects), melancholic type (melancholic versus non-melancholic patients) or resistant depression group (treatment-resistant versus non-treatment-resistant) was based on the importance of each of the immunometabolic and lifestyle variables.

Results: With the application of the algorithm, controls versus patients, such as patients with melancholic symptoms versus non-melancholic symptoms, and resistant versus non-resistant symptoms in the test phase were optimally classified.

The variables that showed greater importance, according to the results of the area under the ROC curve, for the discrimination between healthy subjects and patients with depression were current alcohol consumption (AUC = 0.62), TNF-α levels (AUC = 0.61), glutathione redox status (AUC = 0.60) and the performance of both moderate (AUC = 0.59) and vigorous physical exercise (AUC = 0.58). On the other hand, the most important variables for

classifying melancholic patients in relation to lifestyle habits were past (AUC = 0.65) and current (AUC = 0.60) tobacco habit, as well as walking routinely (AUC = 0.59) and in relation to immunometabolic markers were the levels of CRP (AUC = 0.62) and glucose (AUC = 0.58).

In the analysis of the importance of the variables for the classification of treatment-resistant patients versus non-resistant patients, the systolic blood pressure (SBP) variable was shown to be the most relevant (AUC = 0.67). Other immunometabolic variables were also among the most important such as TNF-α (AUC = 0.65) and waist circumference (AUC = 0.64). In this case, sex (AUC = 0.59) was also relevant along with alcohol (AUC = 0.58) and tobacco (AUC = 0.56) consumption.

Conclusions: The results obtained in our study show that it is possible to predict the diagnosis of depression and its clinical typology from immunometabolic markers and lifestyle habits, using machine learning techniques. The use of this type of methodology could facilitate the identification of patients at risk of presenting depression and could be very useful for managing clinical heterogeneity.

1. Introduction

Depression is a common disease that affects approximately 4% of the world's population, being one of the main causes of disability worldwide (Mathers and Loncar, 2006; World Health Organization, 2017). Although there are effective treatments for major depressive disorder (MDD), a high percentage of patients may suffer from recurrent episodes and many of them are resistant to treatment (Gaynes et al., 2009). In addition, the pathophysiology of MDD is still unknown partly due to the great heterogeneity of depressive symptoms. Therefore, there is an important need for new conceptual frameworks to understand the pathophysiological underpinnings of depression that lead to the development of more effective treatments.

A promising conceptual framework is the study of inflammatory dysregulation in MDD. Inmune alterations in MDD have been reported during decades with strong evidence of an association between an overstimulation of the inmune system and the presence of depressive symptoms (Beurel et al., 2020; Ma et al., 2016; Osimo et al., 2019). High levels of inflammation and oxidative stress (eg, C-reactive protein CRP; tumor necrosis factor alpha, TNF-*α*; 4-hydroxynonenal (HNE); gluta-thione) (Lotrich, 2015; Mazereeuw et al., 2015; Moriarity et al., 2021; Qiu et al., 2021; Zainal and Newman, 2021) as well as metabolic disturbances (i.e. leptin and insulin resistance or dyslipidemia) (Evans et al., 2005) have repeatedly been shown in all patients with MDD. However, these findings are not present in all patients with MDD (Lotrich, 2015; Qiu et al., 2021; Raison and Miller, 2011). Recent theories point to an association between immnunometabolic alterations and specific subtypes of depression, particularly depression with atypical symptoms or symptoms reflecting altered energy intake/expenditure balance (hyperphagia, weight gain, hypersomnia, fatigue, and leaden paralysis) (Milaneschi et al., 2021). Patients with somatic and vegetative symptoms (that is, increased appetite, weight gain, and hypersomnia) (Matza et al., 2003; Quitkin, 2002), present higher levels of CRP (Hickman et al., 2014; Milaneschi et al., 2021; Lamers et al., 2013) which has been shown to be correlated with the duration of the disorder (Karlović et al., 2012). Furthermore, this subtype of patients could have a higher risk of metabolic syndrome, presenting higher values in BMI, waist circumference, triglycerides and HDL-C (Lamers et al., 2013; Lasserre et al., 2017). In depressive patients with melancholic features, it has also been reported an increase in the levels of pro-inflammatory biomarkers compared to non-melancholic patients (Karlović et al., 2012; Lamers et al., 2020).

In addition to the subtype of depression, the inflammatory phenotype has been associated to treatment resistance (Lanquillon et al., 2000; Sluzewska et al., 1997; Uher et al., 2014). Patients with resistant depressive disorder have particular clinical and biological characteristics, such as poor physical health (Maes et al., 2011), chronicity or recurrence of depressive symptoms (Anisman et al., 1999), which could be explained by underlying low-grade inflammation (Strawbridge et al., 2019).

Unhealthy life styles such as sedentarism, smoking or alcohol consumption, could mediate the association between immunometabolic

alterations and depression (Dikalov et al., 2019; Qamar et al., 2019; Powers et al., 2020; Puddey et al., 2019) and could be related to a poor physical health (Boden and Fergusson, 2011; Hoare et al., 2016; Mikkelsen et al., 2017; Prochaska et al., 2017; Puddephatt et al., 2021; Rajan and Menon, 2017; Roberts and Bailey, 2011; Sullivan et al., 2005) resulting in obesity, diabetes or metabolic syndrome (Qiu et al., 2021; Teskey et al., 2018).

The association between immunometabolic disturbances (including inflammation, oxidative stress and metabolic dysfunction) and particular clinical features in depression could constitute an opportunity to address the clinical heterogeneity in depression as well as the underlying pathophysiology.

Machine learning methods are increasingly being used in mental disorder research (Graham et al., 2019; Shatte et al., 2019). This methodology, based on making explicit assumptions about the subtypes of patients and subsequent adjustment of the data to these assumptions, allows the development of models that can contribute to create more homogeneous groups of patients. In addition, this methodology is able to detect high-dimensional complex interactions, not requiring prior knowledge of the possible relationships between variables (Graham et al., 2019).

We aim to classify patients with MDD using machine learning algorithms that take into account immunometabolic biomarkers and lifestyles. In particular we aim to classify subjects into patients with MDD or healthy subjects, patients with melancholic symptoms or without melancholic symptoms and treatment resistant patients or patients that respond to treatment.

2. Method

In this cross-sectional study, a sample of 171 participants was recruited (91 MDD patients and 80 HC). All patients were recruited from primary healthcare centres of Madrid and the outpatients′ psychiatric services of University Hospital La Princesa (Madrid, Spain), Bellvitge University Hospital and Hospital del Mar (Barcelona, Spain). Patients had to meet criteria for a current episode of MDD according to the Diagnostic and Statistical Manual of Mental Disorder 4th Edition (DSM-IV-TR) (American Psychiatric Association, 2000), which was endorsed with the Mini International Neuropsychiatric Interview (MINI) (Ferrando et al., 2000). Sex- and age-matched HC were recruited from the community; absence of current or past major psychopathology was confirmed with the MINI interview.

To be included in the study, patients and HC should meet the following inclusion criteria: 18–69 years old, white persons with European ancestry and ability to understand and to sign the informed consent. The exclusion criteria were: presence of any neurological or inflammatory disorder, use of antibiotic and/or anti-inflammatory treatment, and pregnancy; absence of current or past mental disorders different from MDD and treatment with electroconvulsive therapy (ECT) for the current episode and in the last six months, for MDD patients. The study complies with the principles of the declaration of Helsinki and following the good practice guidelines. The Local Ethics Committees of

each hospital approved the research protocol.

2.1. Demographic and lifestyle variables

Demographic variables assessed for all participants were age, sex, marital status (subjects were classified as: never married, married/partnered, separated/divorced or widowed), years of education and current job status (subjects were classified as: active in work, unemployed, sick leave or retired).

Lifestyle factors explored were tobacco use (subjects were classified as smokers, abstainers and non-ever smokers), alcohol consumption (drinkers, abstainers and non-ever drinkers) and general physical activity measured using the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). The general habits regarding the type of physical activity were carried out by participant self-reports (i.e., walking, moderate physical activity, and vigorous physical activity).

2.2. Metabolic status

Measures of weight and height to obtain the body mass index (BMI) (kg/m^2), waist circumference (cm) and blood pressure (mm/Hg) were conducted at recruitment site by standardized procedures and using the same measurement tools.

According to the guidelines of the Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), the following measures were included as metabolic risk variables: waist circumference and blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)), high density lipoprotein cholesterol (HDL-C), triglycerides (mg/dL), and fasting blood sugar level (FBS) (mg/dL).

2.3. Inmunometabolic and oxidative stress biomarker quantification

A blood draw was performed for quantification of metabolic biomarkers, analysis of oxidative markers (ie, HNE and glutathione redox status), and for analysis of inflammatory markers (TNF-α and CRP). Blood sample was drawn early in the morning (between 8:00 and 10:00 a.m.) upon a fasting night. An indwelling venous catheter was inserted in the antecubital vein.

HNE levels and glutathione redox status as oxidative stress biomarkers, and TNF-α and CRP as inflammatory biomarkers, were quantified. Blood samples were collected in tubes containing ethylenediamine tetra acetic acid (EDTA) for HNE and glutathione, and tubes without additives to collect TNF-α and CRP.

All samples were centrifuged after plasma separation and subsequent storage until quantification analysis. For measuring glutathione redox status, 500 μL of whole blood were immediately treated with N-ethyl-maleimide to block free thiols and proteins and membranes were precipitated with perchloric acid, obtaining the supernatant after centrifugation. The samples were stored at a temperature of −80 °C and were analyzed by the same laboratory, blinded for case and control status.

The following analysis protocol was followed:

1) TNF-α was quantified by solid phase sandwich ELISA assays on the automated AP22 IF BLOT ELITE system (DAS srl) using a commercial invitrogen™ kit. The minimum detectable dose of Hu TNF-α for this commercial kit is 1.7 pg/mL and inter and intra-assay precision <10% in both cases (8.5 and 5.2% respectively).
2) CRP quantification was carried out by using serum samples, under the analytical method of immunoturbidimetry, with a Cobas 8000 analyzer (Roche Diagnostics) with reference values of 0.0–0.5 mg/dL.
3) HNE concentration was quantified in plasma samples by using the OxiSelect HNE adduct competitive ELISA kit (Cell Biolabs, San Diego, CA, USA) using HNE-conjugated bovine serum albumin (HNE-

BSA) as standard (range 1.6–200 μg/mL), following the manufacturer's instructions with and inter and intra-assay precision <15%.
4) Glutathione redox status was calculated by the ratio of oxidized and reduced glutathione (GSSG/GSH) that were determined by mass spectrometry in the Central Service for Support to Experimental Research (SCSIE) at the University of Valencia. The chromatographic system consisted of a Micromass QuatroTM triple-quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with a Zspray electrospray ionization source operating in the positive ion mode with a LC-10A Shimadzu (Shimadzu, Kyoto, Japan) coupled to the MassLynx software 4.1 for data acquisition and processing. Samples were analyzed by reversed-phase UPLC with a C18 Mediterranea SEA column (Teknokroma, Barcelona, Spain) (5.060.21 cm) with 3 mm particle size.

2.4. Clinical variables

For the patient sample, the clinical variables included were: depressive symptoms profile (i.e. melancholic, non-melancholic) measured by the International Neuropsychiatric Interview, MINI (Ferrando et al., 2000) and treatment failures (resistance) assessed by the Thase and Rush scale (Thase and Rush, 1995). Patients who were in stage I according to this scale (lack of response to an adequate trial of a drug) were categorized as non-resistant to treatment and patients who were in stage II (lack of response to two different trials of monotherapy of drugs with different pharmacological profiles), III (stage II plus lack of response to the augmentation of one of the monotherapies) and IV (stage III plus failure of a second augmentation strategy) were categorized as resistant to treatment.

2.5. Data analysis

Demographic variables and immunometabolic biomarkers were compared between HC and MDD patients by means of χ^2 test (or exact F test by the Fisher's exact test) for categorical variables and *t*-tests for continuous variables. The immunometabolic biomarkers underwent loglinear transformation and the missing data were imputed under the multiple imputations procedures (Sterne et al., 2009). Imputation parameters were set at 50 iteration rounds and 10 imputation models under the random forest imputation method. In total, 6.06% of the missing data were imputed.

Cross-validation supervised machine learning algorithms were used to classify participants according to their diagnosis (HC vs. MDD patient); symptoms profile (melancholic vs. non-melancholic) and resistance to treatment (resistant vs. non-resistant). The immunometabolic markers (i.e., waist circumference, SBP, HDL-C, triglycerides, FBS, glutathione, HNE, TNF-α and CRP) and lifestyle factors (i.e., alcohol consumption, tobacco consumption and physical activity) were used as covariates. Continuous variables were scaled to be transformed into a same metric. The response to the dimensions of the categorical variables were dichotomized into yes/no for all of them (i.e. tobacco use: smokers (yes/no) and abstainers (yes/no); alcohol use: drinkers (yes/no) and abstainers (yes/no) and general physical activity: walking (yes/no), moderate physical activity (yes/no) and high physical activity (yes/no).

Classification models were independently estimated by four algorithms: multiple logistic regression, random forest, support vector machines (SVM) with Kernel radial (non-linear decision boundary) and gradient boosting. For all cases, a 10-fold cross-validation rationale was followed, with a training sample of 70% of the sample and the testing sample. Model hyperparameters were tuned across models to optimize the penalization to control for multidimensionality between predictors. More concretely, hyperparameters considered for random forest models were: number of the random features (mtry) was 3,4,5 and 7; minimum node size (min.node.size) = 2,3,4,5,10,15,20 and 30; and spliture function was gini. For SVM hyperparameters tested were sigma (0.001,0.01,0.1,0.5 and 1) and cost (1,20,50,100,200,500 and 700). A

total of 1750 resamples were obtained (5*7 solutions due to hyper-parameter thresholds, 10 folds and five repeated times. For gradient boosting tree models (number of trees = 500,1000 and 2000) shrinkage (0.001,0.01 and 0.1), interaction.depth (), and number minimum observations in nodes (n.minobsinnode) (Anisman et al., 1999; Bilici et al., 2001; Foley et al., 2021) were tested.

Iterative 10-fold-cross-validation was carried out to select the model with the optimal number of predictors under supervised feature selection rationale, basically focused on removing variables without any influence to classify individuals, and rank relevant predictors by relative contribution to outcome explanation. The 10-fold cross-validation, is the most commonly followed method in data mining (Refaeilzadeh et al., 2009) with the outcome variance being lower at more replications, increasing the accuracy of the models (Kuhn and Johnson, 2013; Refaeilzadeh et al., 2009). In addition, this method is preferred with small samples because it can allow stabilizing the models and obtaining a reliable estimate or comparison of performance (Beleites and Salzer, 2008). By this method, the system divides the training sample into 10 training subsets and test subsets of the model, taking the rest as the training set, being different in each iteration, obtaining the final precision and error from the average of the trained models. In addition, 5 repetitions were performed, which implied adjusting the model 10×5 times. In the case of both logistic regression and random forest algorithms feature selection was based on a built-in feature selection rationale (see Gevrey et al., 2003), by which different models with a concrete subset of features are trained to find the combination of features with a better performance. By contrast, the area under the curve (AUC) was also used to determine for feature selection (i.e., the model with a higher AUC value across the relevant pairwise predictor-wise AUCs may show a model with an optimal feature selection) in a model estimated using either the SVM or gradient boosting algorithm (Castro-Martín et al., 2021; Rakotomamonjy et al., 2003).

To measure the classification accuracy across models, the AUC was used to observe the fit of each algorithm. The curve represents the relationship between true positive rates (sensitivity) as a function of false positive rate (1-specificity). The model with a higher AUC was selected, taking into account that this model should also have a hit rate higher than expected by chance, i.e. higher than the baseline level, which is obtained if all observations are assigned to the majority class.

Relative importance of each predictor to classify individuals was estimated, again under the built-in feature selection strategy for both logistic regression and random forest algorithms; and the AUC rationale for the models estimated using either the SVM or gradient boosting.

All data were analyzed using the R Software (foreign, mice, effsize, psych, recipes, scales, and caret packages).

3. Results

Sociodemographic, lifestyles and immunometabolic biomarkers levels of MDD patients and HC are displayed in Table 1. Both samples obtained significant differences in the years of schooling ($t = 3.14$; $p < .001$; $d = 0.52$) and employed status ($\chi^2 = 67.58$; $p < .001$; Cramer's $V = 0.63$) (see Table 1.).

In terms of lifestyles, we observed significant differences between both groups in alcohol consumption ($\chi^2 = 13.01$; $p < .01$; Cramer's $V = 0.28$) and performance of moderate physical exercise ($t = 4.65$; $p < .05$; $d = 0.17$).

71.42% of the MDD patients presented melancholic symptoms and 64.83% were resistant to treatment. In the comparison between melancholic and non-melancholic patients, we only found significant differences in the years of schooling ($t = 2.81$; $p < .01$; $d = 0.65$); in the comparison between treatment resistant patients and not resistant, we observed significant differences in systolic blood pressure ($t = 2.56$; $p < .01$; $d = 0.53$). No other immunometabolic or lifestyle variables showed significant differences between the groups of patients (see Table 2).

Table 1

Demographics, clinical and health-related variables of HC and MDD patients.

Variables	Healthy controls	MDD patients	t-F/χ^2	Effect size
	$N = 80$	$N = 91$		
Female (%)	67.50	71.43	−0.15	−0.04
Age, years	49.12 (10.24)	50.64 (10.18)	0.97	0.15
Years of schooling	15.91 (4.96)	13.20 (5.50)	−3.14	−0.52***
Employment Status (%)			−67.58	−0.63***
Active in Work	86.25	26.37		
Unemployed	10.00	20.88		
Sick Leave	1.25	48.35		
Retired	2.50	4.40		
Marital status (%)			−3.07	−0.13
Never married	23.75	24.44		
Married/partnered	60.00	56.67		
Separated/divorced	8.75	15.55		
Widowed	7.50	3.33		
Tobacco use (%)			−4.94	−0.17
Smokers	17.50	29.67		
Non-ever smokers	51.25	36.26		
Abstinent	31.25	34.06		
Alcohol consumption (%)			−13.01	−0.28**
Drinkers	63.75	37.36		
Non-ever drinkers	35.00	56.04		
Abstinent	1.25	6.59		
Walking (yes%)	91.25	86.81	−0.46	−0.07
Moderate PA (yes%)	55.00	37.36	−4.65	−0.17*
High PA (yes%)	28.75	15.38	−3.73	−0.16
BMI	26.01 (4.50)	26.62 (4.92)	0.85	0.13
SBP (mm/Hg)	2.10 (0.06)	2.08 (0.06)	−1.67	−0.25
DBP (mm/Hg)	1.90 (0.06)	1.88 (0.07)	−1.41	−0.19
Waist (cm)	1.94 (0.07)	1.96 (0.06)	1.57	0.25
HDL-C (log)	1.77 (0.12)	1.77 (0.13)	−0.01	−0.01
Glucose (log)	1.98 (0.06)	1.97 (0.07)	−0.91	−0.14
Triglycerides (log)	1.97 (0.23)	1.98 (0.20)	0.51	0.08
TNF-α (log)	0.84 (0.21)	0.79 (0.23)	−1.30	−0.19
CRP (log)	−0.98 (0.43)	−0.79 (0.38)	3.07	0.48**
HNE (log)	1.17 (0.28)	1.29 (0.35)	2.22	0.49*
GSSD/GSH (log)	0.48 (0.45)	0.36 (0.45)	−1.48	−0.22
Melancholic symptoms (%)		71.43		
Treatment Resistant (%)		64.83		

Note. Percentage of cases are displayed for dichotomous and categorical variables. Means and standard deviation (between brackets) are displayed for continuous variables. Effect size estimates (Cohen's *d* for continuous outcomes and Cramer's *V* for non-continuous outcomes).

BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HDL-C = High-density lipoprotein cholesterol, TNF-α = Tumor necrosis factor, CRP = C-reactive protein, HNE = 4-Hydroxynonenal, GSSG = Oxidized glutathione, GSH = Reduced glutathione.

* $p < .05$; ** $p < .01$; *** $p < .001$.

3.1. HC vs. MDD patients

Although the models derived from the four algorithms showed an adequate ability to correctly classify a significant number of participants, above the baseline level (53%), the model with the highest classification accuracy was estimated using the radial SVM (AUC = 0.65) (see Fig. 1.a.), with hyperparameters C = 20 and sigma = 0.50 (see Table S1.b). In relation to the importance of the variables, we found that lifestyles such as current alcohol consumption (AUC = 0.62) and moderate (AUC = 0.59) and vigorous physical exercise (AUC = 0.58) are the variables that are most related to the condition of being a MDD patient or a control subject. Regarding the immunometabolic and oxidative stress markers, TNF-α (AUC = 0.61), glutathione redox status (AUC = 0.60), waist circumference (AUC = 0.57) and CRP (AUC = 0.46) were the most relevant (see Fig. 2.a.).

Table 2

Demographics, clinical and health-related variables of melancholic and non-melancholic patients and resistant and non-resistant patients.

Variables	Melancholic N = 65	Non melancholic N = 26	t-z/χ²	Effect size	Resistant N = 59	Non resistant N = 32	t-F/χ²	Effect size
Female (%)	69.23	76.92	0.22	0.08	69.49	75.00	0.10	0.06
Age, years	50.41 (9.96)	51.19 (10.89)	0.33	0.07	51.20 (10.31)	49.59 (10.01)	−0.71	−0.15
Years of schooling	12.39 (4.56)	15.42 (5.29)	2.81	0.65**	13.39 (5.46)	12.84 (3.95)	−0.50	−0.11
Employment Status (%)			0.58	0.05			3.68	0.20
Active in Work	27.69	23.08			20.34	37.50		
Unemployed	20.00	23.07			20.34	21.87		
Sick Leave	47.69	50.00			54.24	37.50		
Retired	4.61	3.85			5.08	3.12		
Marital status (%)			6.98	0.29			5.85	0.25
Never married	23.44	26.92			27.59	18.75		
Married/partnered	64.06	38.61			48.27	71.87		
Separated/divorced	10.94	26.92			20.69	6.25		
Widowed	1.56	7.69			3.45	3.12		
Tobacco use (%)			0.44	0.07			4.65	0.22
Smokers	27.69	34.61			25.42	37.50		
Non-ever smokers	36.92	34.61			44.07	21.87		
Abstinent	35.38	30.77			30.51	40.62		
Alcohol consumption (%)			4.69	0.23			1.62	0.13
Drinkers	30.77	53.84			33.90	43.75		
Non-ever drinkers	63.08	38.46			57.63	53.12		
Abstinent	6.15	7.69			8.47	3.12		
Walking (yes%)	87.69	84.61	0.01	0.04	84.74	90.62	0.22	0.08
Moderate PA (yes%)	38.46	34.61	0.01	0.04	32.20	46.87	1.33	0.14
High PA (yes%)	15.38	15.38	0	0	13.56	18.75	0.12	0.07
BMI	26.93 (4.95)	25.84 (4.85)	−0.95	−0.22	26.66 (4.92)	26.55 (4.98)	−0.09	−0.02
SBP (log)	2.08 (0.06)	2.09 (0.05)	−0.51	−0.13	2.10 (0.06)	2.07 (0.06)	−2.43	−0.53*
DBP (log)	1.87 (0.07)	1.89 (0.06)	0.80	0.17	1.88 (0.07)	1.88 (0.06)	0.07	0.01
Waist (log)	1.96 (0.06)	1.93 (0.08)	−1.72	−0.30	1.96 (0.07)	1.95 (0.06)	−0.80	−0.21
HDL-C (log)	1.78 (0.14)	1.76 (0.13)	−0.51	0.11	1.77 (0.13)	1.77 (0.14)	−0.28	0.06
Glucose (log)	1.96 (0.07)	1.98 (0.07)	1.04	0.24	1.97 (0.04)	1.96 (0.06)	−0.86	0.18
Triglycerides (log)	1.98 (0.20)	2.01 (0.19)	0.85	0.19	1.98 (0.19)	1.99 (0.21)	0.22	0.04
TNF-α (log)	0.78 (0.23)	0.83 (0.31)	1.02	0.23	0.77 (0.22)	0.83 (0.24)	1.21	0.26
CRP (log)	−0.76 (0.39)	−0.86 (0.34)	−1.06	−0.25	−0.76 (0.40)	−0.84 (0.34)	−0.97	−0.22
HNE (log)	1.27 (0.35)	1.32 (0.34)	0.56	0.13	1.29 (0.35)	1.27 (0.36)	−0.26	−0.06
GSSG/GSH (log)	0.28 (0.54)	0.55 (0.57)	2.09	0.48	0.38 (0.57)	0.31 (0.56)	−0.55	−0.12
Melancholic symptoms (%)					66.10	81.25		
Treatment Resistant (%)	60.00	76.92						

Note. Percentage of cases are displayed for dichotomous and categorical variables. Means and standard deviation (between brackets) are displayed for continuous variables. Effect size estimates (Cohen's *d* for continuous outcomes and Cramer's *V* for non-continuous outcomes).

BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HDL-C = High-density lipoprotein cholesterol, TNF-α = Tumor necrosis factor, CRP = C-reactive protein, HNE = 4-Hydroxynonenal, GSSG = Oxidized glutathione, GSH = Reduced glutathione.

* $p < .05$; ** $p < .01$; *** $p < .001$.

3.2. Melancholic vs non-melancholic patients

For classification according to the type of depressive symptoms (i.e., melancholic vs. non-melancholic patients) the algorithm that showed higher accuracy was the SVM model (AUC = 0.76) (see Fig. 1.b.) with C = 20 and sigma = 0.50 as hyperparameters (see Table S3.b). The study of the importance of variables in the classification of patients with melancholic symptoms versus patients with non-melancholic symptoms, showed that lifestyles had a great importance in the generation of the model, being able to highlight the past and current tobacco habit (AUC = 0.65, AUC = 0.60) and the habit of walking (AUC = 0.59).On the other hand, in terms of immunometabolic markers, CRP (AUC = 0.62) and glucose (AUC = 0.58) values were notable, being among the first five relevant predictors (see Fig. 2.b.)

3.3. Resistant vs non-resistant patients

For differentiation between treatment resistant and non-resistant patients, both gradient boosting and SVM an optimal fit value (above the baseline level = 64%). The model selected was SVM (AUC = 0.65) (see Fig. 1.c.) with C = 1 and sigma = 0.10 as hyperparameters (see Table S5.b) due to its better performance in the previous predictions (i. e., controls vs. MDD patients and melancholic vs. non-melancholic patients).

In the analysis of the importance of the variables in the classification model of patients with treatment-resistant or non-treatment-resistant depression, the SBP variable was shown to be the most relevant (AUC = 0.67). Other immunometabolic variables were also among the most important such as TNF-α (AUC = 0.65) and waist circumference (AUC = 0.64). In this case, sex (AUC = 0.59) was also relevant along with alcohol (AUC = 0.58) and tobacco (AUC = 0.56) consumption (see Fig. 2.c).

4. Discussion

This study aimed to classify patients with MDD using machine learning algorithms that took into account immunometabolic biomarkers and lifestyles. Automatic classification of subjects into MDD patients, melancholic subtye and treatment resistant was successfully performed through machine learning algorithms according to immunometabolic biomarkers and lifestyles.

To perform this classification, different cross-validation supervised machine learning algorithms were carried out using different automatic classification methods, being the support vector machine (SVM) classification method the best method to optimally discriminate to which class the data belong to. Specifically, the SVM assures that the chosen hyperplane is the one that best separates the classes, following the principle of maximum margin (Vapnik, 1998), guaranteeing the best

a. HC and MDD patients.
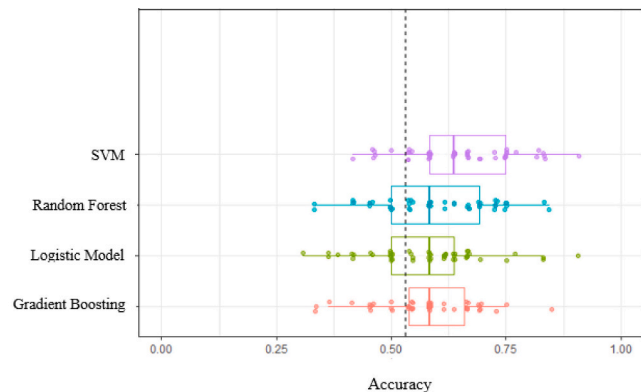
b. Melancholic and non-melancholic patients.
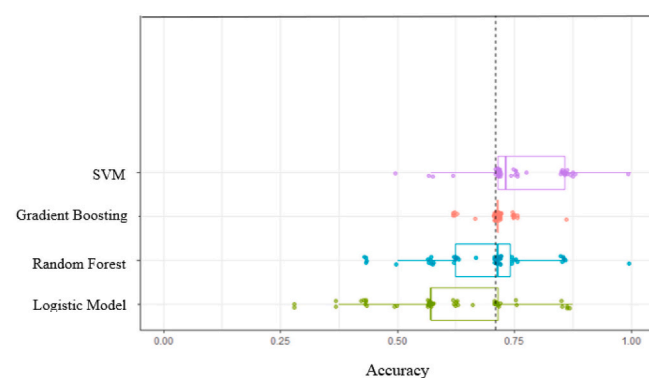
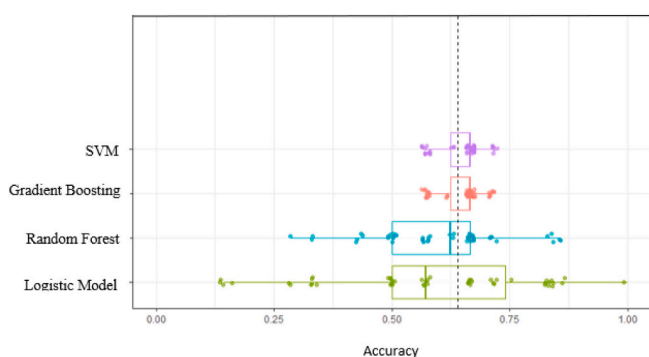**c.** Resistant and non-resistant patients.

Fig. 1. Comparison of accuracy of algorithmic models.
Note. Each of the figures shows a comparison of the models made.
The dashed line represents the baseline level, which is obtained if all observations are assigned to the majority class in each of the comparisons made (i.e. 1.a = 0.53, 1.b = 0.71 and 1.c = 0.64).
SVM = support vector machine.

generalization performance in the classification of new data.

The classification algorithms allowed an optimal classification between MDD patients and HC. Regarding the inflammatory factors, the pro-inflammatory cytokines TNF-α and CRP were relevant for the differentiation of the group of patients from the HC group and regarding the metabolic risk variables, the waist circumference differentiated between both groups.

The inflammatory disturbances that exhibit MDD patients could be the consequence of an hyperactivation of the hypothalamic pituitary adrenal (HPA) axis (Fiksdal et al., 2019) motivated by chronic stress (Horowitz et al., 2020; Liu et al., 2017), impacting on the production of

antioxidants through the dysregulation of the glucocorticoid production (Zalachoras et al., 2020). Thus, the increased production of glutathione, TNF or CRP in MDD patients (Beurel et al., 2020; Ma et al., 2016; Mazereeuw et al., 2015; Osimo et al., 2019; Rae and Williams, 2017; Zalachoras et al., 2020) is an important factor in the differentiation between healthy subjects and MDD patients.

Waist circumference has been shown to be relevant in the distinction between healthy subjects and MDD patients. There is evidence that the association between depression and obesity is stronger in subjects with abdominal obesity, being the risk of depression approximately 50% in the presence of abdominal obesity (Xu et al., 2011). Abdominal adiposity is characterized by the accumulation of visceral fat, more related to metabolic dysregulations and with a greater effect on inflammation (Xu et al., 2011).

Patients' lifestyles seem to be an important mediator of the relationship between certain medical comorbidities such as obesity and depression (Hoare et al., 2016; Mikkelsen et al., 2017; Prochaska et al., 2017; Rajan and Menon, 2017; Roberts and Bailey, 2011). Certain risk behavior patterns such as a sedentary lifestyle, smoking or alcohol consumption are often associated to depression (Hoare et al., 2016; Mikkelsen et al., 2017; Prochaska et al., 2017; Rajan and Menon, 2017; Roberts and Bailey, 2011). We have found that both alcohol consumption and physical exercise are important when classifying subjects as having a MDD diagnosis. We have found that both alcohol consumption and physical exercise are important in classifying subjects with a diagnosis of MDD. In our study, not consuming alcohol was associated with a diagnosis of MDD, with a higher percentage of non-ever drinkers. This could be explained as an exclusion criterion was dual pathology and therefore the consumption of alcohol in MDD patients without dual pathology may be diminished due to the use of psychopharmacological treatments. Besides, we have found that patients performed less moderate physical exercise. Depression and lack of physical activity have a two-way relationship, thus depressive symptoms such as lack of energy, apathy or feeling of ineffectiveness are associated with less physical activity (Vancampfort et al., 2015) and lower levels of physical activity carry a greater risk of having depression which suggests that exercise could improve depressive symptoms and quality of life of patients (Lee et al., 2021; Mammen and Faulkner, 2013; Martland et al., 2020; Schuch et al., 2015). Although the evidence supporting the association between the performance of physical exercise and the decrease of peripheral inflammatory markers is still scarce and heterogeneous (Fernandes et al., 2021), it is plausible that the beneficial effect of physical exercise on MDD could be mediated by its ability to reduce inflammation (Shao et al., 2021) and induce an anti-inflammatory environment (Gleeson et al., 2011; Petersen and Pedersen, 2005).
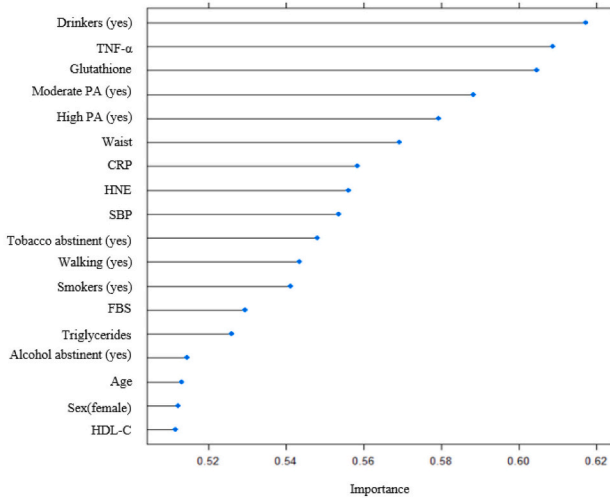
Regarding the classification of patients with melancholic symptoms versus patients without melancholic symptoms, the algorithm also achieved an optimal classification, supporting the theory that both subtypes of depression have different characteristics (Dold et al., 2021). For this classification, the most important immunometabolic variables, were CRP levels and blood sugar levels.

Our results are in line with previous studies, in which differences were observed between melancholic and non-melancholic patients in the levels of proinflammatory biomarkers.

In previous studies, it has been observed that patients with symptoms unrelated to the melancholic subtype (ie increased weight, hypersomnia, leaden paralysis and low energy, called energy-related symptom dimension), had higher levels of CRP than patients with melancholic symptoms (Lamers et al., 2020), this fact has been attributed to a later age of onset of depression with melancholic symptoms, so it is possible that visible elevations in CRP levels have not yet occurred (Yang et al., 2018).

In fact, energy-related dimension symptoms have been related to a greater extent to a higher body mass index (BMI) and metabolic problems, so it is consistent that these types of patients have higher levels of inflammatory markers, since obesity and impaired metabolism are
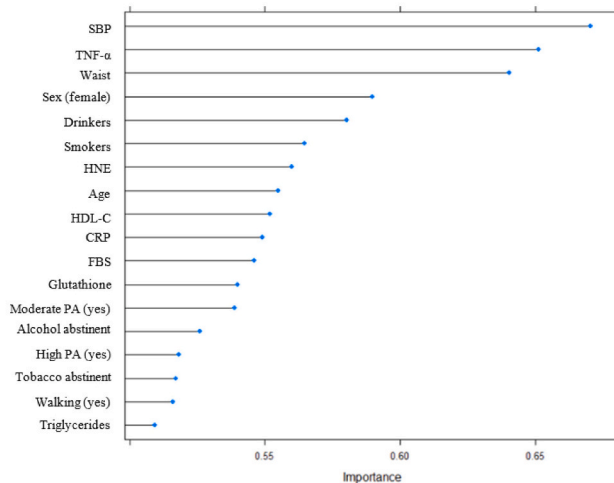
a. HC and MDD patients.

b. Melancholic and non-melancholic patients.
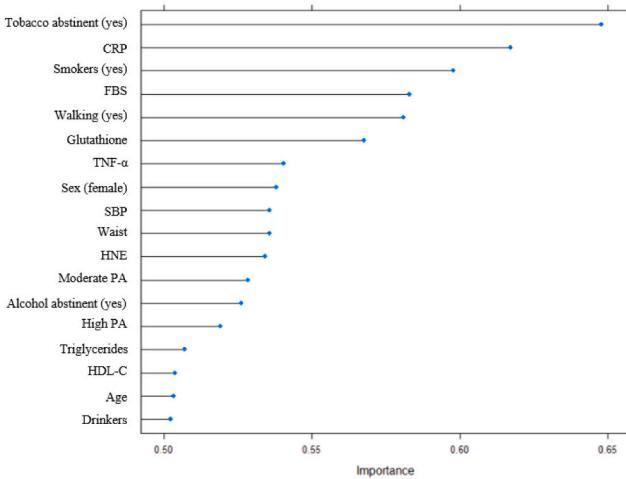
c. Resistant and non-resistant patients.

(caption on next column)

Fig. 2. Variable importance in SVM models.
Note. The plot includes the classification sensitivity (i.e., proportion of individuals with the target condition and correctly classified) on the y-axis and 1 - specificity (i.e., proportion of individuals without the target condition and correctly classified) on the x-axis. Each of the lines represents the value of the area under the curve of each of the predictors considered in the model. The predictors are ordered in descending order taking into account this score.
TNF-α = tumor necrosis factor. PA = physical activity. CRP = C-reactive protein. HNE = 4-hydroxynonenal. SBP = systolic blood pressure. FBS = fast blood sugar. HDL-C = high density lipoprotein cholesterol.

related to low-grade inflammation (Lamers et al., 2013). This difference in the inflammatory state may cause these patients to experience other types of consequences in their quality of life and, at the same time, they are patients in whom it is worth analyzing other types of interventions that include anti-inflammatory measures (Foley et al., 2021).

We have also observed in our study that patients with non-melancholic symptoms present higher glucose levels than patients with melancholic depression, which would be related to the greater immunometabolic alteration of these patients. This is consistent with previous research, in which no significant differences in glucose levels were found between patients with melancholic symptoms and healthy subjects (Lamers et al., 2013; Lasserre et al., 2017). It is important to take this fact into account, since if we carry out studies without differentiating according to subtypes, we can reach erroneous conclusions.

According to our model, glucose levels are an important variable to take into account in the classification of melancholic and non-melancholic patients. Therefore, non-melancholic patients would be at a greater risk of developing insulin resistance and diabetes, in addition to the subsequent cardiovascular risk that it could entail (Evans et al., 2005).

In addition to the immunometabolic markers, two variables related to lifestyles turned out to be relevant for the classification of patients in melancholic and non-melancholic: the current and past smoking habit and the habit of walking. In general, patients with depression are known to be more likely to smoke and relapse, along with lower rates of quitting (Mathew et al., 2017; Weinberger et al., 2017) and a greater tendency to be sedentary (Vancampfort et al., 2015). In our sample, non-melancholic patients are the ones with a greater tendency to have unhealthy lifestyle habits, which could be related to the greater presence of immunometabolic alterations and, ultimately, worse health status of these patients (Maddatu et al., 2017; Van Gool et al., 2003).

Regarding the classification of resistant and non-resistant patients, the algorithm was also able to correctly classify patients. The variables that turned out to be most relevant after our analysis were the immunometabolic markers: TNF-α, systolic blood pressure, and waist circumference.

The proinflammatory cytokine TNF-α has been associated with significantly post-treatment symptom improvement in responders (Lanquillon et al., 2000). Proinflammatory cytokines such as TNF-α are known to alter the metabolism and release of serotonin in the central nervous system, a neurotransmitter involved in the regulation of sleep, appetite and emotional state (Nestler et al., 2001). Among other cytokines, TNF-α is involved in facilitating the activity of the serotonin transporter, so increases in the levels of this cytokine can hinder the action of certain antidepressant drugs such as selective serotonin reuptake inhibitors (SSRI) (Zhu et al., 2006). These findings indicate the possibility that TNF-α may act in the CNS as a short-term neuromodulator (Zhu et al., 2006). Hence, the measurement of this cytokine could become relevant for depressed patients with multiple failed antidepressant treatment trials in their current depressive episode (Haroon et al., 2018).

We have also found that both SBP and waist circumference are two important variables when classifying patients according to their resistance to treatment. Resistant depression has a worse course than non-resistant depression, with a higher rate of recurrence and

chronification of the disease in these patients (Anisman et al., 1999). This worse evolution may favor the association between depression and poorer physical health (Maes et al., 2011) and also chronicize risk behaviors with respect to health habits (Hoare et al., 2016; Mikkelsen et al., 2017; Prochaska et al., 2017; Rajan and Menon, 2017; Roberts and Bailey, 2011). In this way, patients with resistance to treatment have higher morbidity (Li et al., 2019) and comorbidity with metabolic diseases (Godin et al., 2019).

Since the Framingham study in which cardiovascular risk factors were analyzed (Mahmood et al., 2014), it is known that there is a direct association between blood pressure and the risk of cardiovascular problems, also observing how isolated systolic hypertension was a powerful predictor of cardiovascular diseases (Kannel et al., 1980). In our sample, resistant patients have significantly higher levels of SBP compared to non-resistant patients, reinforcing the idea that they may have a higher risk of health problems in the future.

Gender was also a relevant variable in the classification algorithm for resistant and non-resistant patients. Although at the moment there is no clear consensus on whether there are differences in efficacy related to sex in antidepressant treatment (Sramek et al., 2016), it has been observed that gender differences at the metabolic and hormonal levels affect pharmacokinetics of antidepressant treatment administered orally (Sramek et al., 2016), observing a differential response according to sex depending on the treatment used (Davidson and Pelton, 1986; Vermeiden et al., 2010).

Regarding the limitations of the study, it should be noted that the analyses were performed using a relatively limited sample size. Although the hyperparameter optimization process was carried out in the present work, small sample sizes can lead to overfitting, a common problem in the use of machine learning techniques, which can limit the generalization of results (Graham et al., 2019).

Regarding data collection in the variables of healthy lifestyle, tobacco use and physical activity measures are self- reported. Self-reported measures may include biases in the study and in subsequent studies it would be advisable to objectively record these sets of variables. On the one hand, taking records of the type of activity carried out by the subjects and time using heart rate monitors or accelerometers and, on the other hand, regarding tobacco use taking records of urinary cotinine concentrations and determination of exhaled carbon monoxide (eCO) level. Also, nicotine consumption was only collected through the number of cigarettes consumed per day. The use of other devices such as nicotine patches would be advisable in future studies.

The study opens a line of research in the use of machine learning, an underused tool in the field of mental health to date, for the study of immunometabolic agents in relation to the clinical variables of MDD.

5. Conclusions

Depression is a highly prevalent mental disorder and a leading cause of disability worldwide that entails high health care costs. The heterogeneity inherent to depression hinders progress in research and treatment. The use of statistical techniques to accurately classify patients has important research and clinical implications. Through this study, using a machine learning approach, we intended to show if immunometabolic and lifestyle variables can be useful to classify major depression patients. Our results have important implications in clinical settings as the identification of unhealthy lifestyles and immunometabolic disturbances can guide and help clinicians in the management of clinical depression.

On the other hand, our work demonstrates the potential of using machine learning algorithms to address depression and especially which type of alggorithms produce the best performance in doing so. Importantly, the possible refinement of such techniques may in the future help mental health professionals to redefine mental disorders in an objective way, being able to identify patients and their prognosis according to risk factors determined as predictive variables and in turn to personalize treatments according to patients' characteristics, thus making them more effective (Graham et al., 2019; Shatte et al., 2019). Different branches of medicine (i.e. ophthalmology, radiology…) already take advantage of the strengths of artificial intelligence (i.e. fast pattern analysis of large datasets) (Graham et al., 2019), our work being one of the few in the literature using these techniques in the field of mental health and specifically depression.

Author contributions

Pilar Lopez-García, Pilar Alvarez and Virginia Soria designed the study and wrote the protocol. Yolanda Sánchez-Carro and Alejandro de la Torre performed the statistical analyses. Yolanda Sánchez-Carro managed the literature searches and wrote the first draft of the manuscript, which was supervised by Pilar Lopez-García.

Itziar Leal-Leturia, Pilar Alvarez, Alba Toll, Victor Pérez-Solà, Virginia Soria, Neus Salvat-Pujol, Mikel Etxandi, Aida de Arriba-Arnau and Mikel Urretavizcaya participated in the recruitment. Yolanda Sánchez Carro, Pilar Alvarez, Clara Massaneda, Alba Toll, Virginia Soria and Mikel Urretavizcaya administered the psychiatric interviews and psychometric scales. Antonio Martínez-Ruiz, Raquel Ferreiros-Martinez, Salvador Pérez, Juan Sastre carried out the processing and analysis of biological samples. All authors contributed to the interpretation and discussion of the results and have approved the final manuscript.

Ethical statement

The study was approved by the Ethical Committee of Clinical Research and was in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained after complete description of the study to the subjects.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest regarding this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.pnpbp.2022.110674.

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