Predicting depressive symptoms in middle-aged and elderly adults using sleep data and clinical health markers: a machine learning approach

Stephania Ruth Basilio Silva Gomes [a], Malcolm von Schantz [b], Mario Leocadio-Miguel [a]

[a] Department of Physiology and Behavior, Federal University of Rio Grande Do Norte, Natal, Rio Grande do Norte, Brazil.

[b] Faculty of Health and Life Sciences, Northumbria University, Newcastle, UK.

*Corresponding author: mario.miguel@ufrn.br

Highlights

- Sleep data facilitates the prediction of depressive symptoms in middle-aged and older adults.
- Daytime sleepiness is an important predictor of depressive symptoms.
- XGBoost outperforms other machine learning (ML) models in the prediction of depressive symptoms.
- ML models to predict depressive symptoms facilitate the screening of depression.

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Abstract

Objectives: Comorbid depression is a highly prevalent and debilitating condition in middle-aged and elderly adults, particularly when associated with obesity, diabetes, and sleep disturbances. In this context, there is a growing need to develop efficient screening methods for cases based on clinical health markers for these comorbidities and sleep data. Thus, our objective was to detect depressive symptoms in these subjects, considering general biomarkers of obesity and diabetes and variables related to sleep and physical exercise through a machine learning approach. **Methods:** We used the National Health and Nutrition Examination Survey (NHANES) 2015-2016 data. Eighteen variables on self-reported physical activity, self-reported sleep habits, sleep disturbance indicative, anthropometric measurements, sociodemographic characteristics and plasma biomarkers of obesity and diabetes were selected as predictors. A total of 2,907 middle-aged and elderly subjects were eligible for the study. Supervised learning algorithms such as Lasso penalized Logistic Regression (LR), Random Forest (RF) and

Extreme Gradient Boosting (XGBoost) were implemented. **Results:** XGBoost provided greater accuracy and precision (87%), with a proportion of hits in cases with depressive symptoms above 80%. In addition, daytime sleepiness was the most significant predictor variable for predicting depressive symptoms. **Conclusions:** Sleep and physical activity variables, in addition to obesity and diabetes biomarkers, together assume significant importance to predict, with accuracy and precision of 87%, the occurrence of depressive symptoms in middle-aged and elderly individuals.

Keywords: Depressive symptomatology; Cardiometabolic syndrome; Sleep variables.

Abbreviations

A

Accuracy

AUC

Area under curve

ACTH

Adrenocorticotropic hormone

BMI

Body mass index

CRP

C-reactive protein

CORT

Corticosterone

EDS

Excessive daytime sleepiness

FA

Frequency absolute

FR

Frequency relative

GPAQ

Global physical activity questionnaire

HPA

Hypothalamic-pituitary-adrenal

HDL

High-density lipoprotein

Hb A1c

Glycated hemoglobin

L

Logistic regression

MDD

Major depressive disorders

ML

Machine learning

NPV

Negative predictive value

NHANES

National Health and Nutrition Examination Survey

NCHS

National Center for Health Statistic

PC

Precision

PA

Physical activity

PHQ-9

Patient health questionnaire

PPV

Positive predictive value

RF

Random forest

SA

Sedentary activity

SD

Sleep duration

TC

Total cholesterol

XGBoost

Extreme gradient boosting

5-HT1A

Serotonin receptors

1. Introduction

Depression is one of the most prevalent mental disorders, affecting a third of a billion people in the world [1]. Importantly, the prevalence of depressive symptoms in middle-aged and elderly adults is high, affecting their quality of life and increasing healthcare spending [2]. The coexistence of multiple comorbidities is common among older adults and there is evidence of a bidirectional association between multimorbidity and depression. For example, the prevalence of depression increases by 37.97% in elderly and middle-aged individuals facing more than three chronic conditions when compared to healthy volunteers [3].

Obesity is an example of a chronic condition that not only shares a common biological mechanism, but also displays a bidirectional relationship with depression, particularly in women [4]. Anthropometric measurements, such as the Body Mass Index (BMI) and the Waist Circumference (WC), are widely adopted to assess general and abdominal obesity, respectively. Both BMI and WC are increased in subjects presenting depressive symptoms when compared to healthy individuals [5]. C-Reactive Protein (CRP), an indicator of peripheral inflammatory processes, is also an indirect marker of obesity with the potential to predict depression. CRP serum concentration is higher in both obese and depressed individuals [6]. Moreover, in a predictive scenario, CRP can differentiate cases of unipolar and bipolar depression [7]. Furthermore, higher levels of CRP are significantly associated with the severity of depression in women [8].

In addition, the lipid profile, represented by high concentrations of total serum cholesterol (TC) and reduced levels of high-density lipoprotein (HDL), is an important marker of obesity in the metabolic syndrome, associated with a higher risk of developing cardiovascular diseases [9]. The same pattern in HDL levels was associated with long-term depression and long-term depressive symptomatology [10,11]. However, reduced levels of TC are associated with depressive symptoms, especially in middle-aged and elderly men [12,13].

Again, when considering the multicomorbid nature of the depressive disorder, researchers have shown that diabetes is also an important risk factor for the development of depression [14]. Moreover, an improvement in glycemic control from 10% to 25% is associated with a decrease in the prevalence of depression [15]. Finally, the elevation of glycated hemoglobin (HbA1c), frequently used as a biomarker of diabetes and pre-diabetes, also predicts depression [16].

Delayed sleep phase [17], instability in sleep onset and/or offset [18], and reduction of the amplitude of multiple circadian rhythms [19,20] are related to depression. In addition, individuals experiencing depression are also often concurrently affected by sleep disorders, such as excessive daytime sleepiness (EDS), which appears to be a common symptom of depression [21]. Interestingly, however, the reduction in nocturnal sleep duration, which is usually associated with EDS, seems to be irrelevant to predicting depression. However, a recent meta-analysis showed that short sleep duration, per se, is associated with the risk of depression [22]. Furthermore, reduced mean sleep duration can predict an increase in depressive symptoms when presented over a period of at least two weeks [23].

Importantly, EDS and insufficient sleep duration result in increased sedentary behavior and reduced physical activity (PA) levels. PA levels are reduced as a function of sleep duration

in subjects with EDS [24]. Furthermore, a more sedentary lifestyle is associated with a higher risk of developing major depressive disorder (MDD) and this relationship is mediated by sleep disorders in general [25]. In addition, subjects with depression tend to perform recreational physical activities less frequently and spend less time on moderate to vigorous activities [26].

Given the increasing difficulty and importance of detecting depression, particularly in middle-aged adults and the elderly, fast and accurate screening methods are needed [27]. Depression screening is usually based on questionnaires and self-report scales, covering questions about sociodemographic characteristics, risk factors and comorbid medical conditions associated with depression [28]. Moreover, interpretation issues and the lack of more objective clinical data may explain the low detection rate of depression found in primary care settings, for example [29]. In this scenario, the application of state of art statistics based on artificial intelligence, such as machine learning (ML), promises to revolutionize clinical practice in psychiatry by enabling the differential diagnosis of depression based on objective, ordinary clinical data [30]. Rather than solving inference problems and understanding the relationship between variables, ML algorithms can learn directly from data and search for complex, non-linear, patterns to enable prediction [31].

Therefore, the objective of the study was to predict the occurrence of depressive symptoms in middle-aged and elderly adults through sleep-related variables, levels of physical activity, anthropometric measures, obesity, and diabetes biomarkers, using a machine learning approach (ML). In addition, we aim to evaluate the potential of multiple predictive variables, together and individually, in predicting the occurrence of depressive symptoms.

2. Methods

Database

Data was retrieved from the National Health and Nutrition Examination Survey (NHANES), biennial period (2015-2016). NHANES is a study program of the National Center for Health Statistics (NCHS) aimed at assessing the health and nutritional status of individuals in the United States, compiling data from a combination of questionnaires and clinical examinations, supporting researchers around the world with an interest in epidemiological studies and aimed at understanding public health problems [32].

Eligible Sample

A total of 2,907 middle-aged and elderly subjects, participants of NHANES (2015-2016), with and without depressive symptoms, were eligible for and included in the present study.

Measures of depressive symptoms

To assess the occurrence of depressive symptoms, we extracted responses from the Patient Health Questionnaire (PHQ-9). This instrument delimits different cut-off points to classify the degree of severity of depressive symptoms into different levels: no depression (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27) [33]. In the study, two cut-off points were determined to classify individuals according to the absence or presence of depressive symptoms. Thus, the established scoring ranges were 0-4 and 5-27, respectively.

Selection of predictor variables (features)

The variable selection was guided by the literature review of depression and its comorbidities. In total, 18 variables were selected, distributed into 7 distinct resource axes: (1) self-reported physical activity (the occurrence of moderate or vigorous recreational activities and sedentary activity (SA)), (2) self-reported sleep habits (sleep onset, sleep offset and sleep duration (SD)), (3) indicative of sleep disturbance (excessive daytime sleepiness), (4) anthropometric measurements (weight, WC and BMI), (5) plasma biomarkers of obesity (C-reactive protein (CRP), total cholesterol (TC) and high-density lipoprotein (HDL), (6) biomarker of diabetes (glycated hemoglobin (HbA1c) and (7) sociodemographic characteristics (sex and age).

Measures of predictor variables

The GPAQ - Global Physical Activity Questionnaire [34] provided data on the prevalence of physical activity in the recreational context, from moderate to vigorous level (at least 10 minutes in a typical week), as well as the time allocated in sedentary activities on a normal day, especially sitting and resting.

The assessment of sleep habits and EDS was established through general self-report questionnaires. Participants reported their usual bedtime, wake-up time and sleep duration on weekdays and workdays. EDS was based on the volunteer's perception of the frequency of diurnal excessive sleepiness in the last 30 days. Through a reference scale the EDS was

classified as: never, rarely (once a month), sometimes (2-4 times a month), often (5-15 times a month) and almost always (16-30 times a month).

Data on the age and sex of participants were acquired from a sociodemographic survey. The anthropometric variables included weight (kg), waist circumference (cm) and BMI (kg/m^2).

To assess plasma biomarkers, such as high-sensitivity CRP, CT and HDL, minimum blood detection limits were determined: 0.11 mg/l, 3mg/dl and 4mg/dl, respectively. Glycated hemoglobin data was obtained from accurate measurements of its stable form (HbA1c) in relative percentages. More details on data collection and processing can be found in the NHANES website (https://www.cdc.gov/nchs/nhanes).

Descriptive and inferential analysis of the eligible sample

Data were submitted to a descriptive statistical routine, considering measures of central tendency (mean and median) and standard deviation for quantitative variables. Furthermore, the normality of these features was verified using the Shapiro-Wilk test. Absolute and relative frequencies for all levels of nominal categorical predictor variables were calculated, as well as for the binary target class of prediction.

Spearman's correlation test was applied to assess the existence of a linear association between predictor variables related to sleep habits, anthropometric measurements, obesity/diabetes plasma biomarkers, in addition to age and the level of depressive symptoms. To investigate whether the groups of participants with and without depressive symptoms differ in terms of the frequency of daytime sleepiness, physical activity at different levels in a recreational context, and gender, the chi-square test of association (independence) was used and the frequency of observed and expected participants at each attribute level was calculated, assuming independence between these variables. In addition, the same test was used to compare possible differences in sleep onset and sleep offset time frequencies between the groups.

To assess whether individuals with and without depressive symptoms vary in terms of age, BMI, TC, CRP, HbA1c, HDL, SA, SD, sleep onset, sleep offset, WC and weight, the Kruskal-Wallis H test was applied.

Supervised machine learning in predicting depressive symptoms

To predict the occurrence of depressive symptoms, based on the predictive features, we developed different supervised machine learning models following four steps [35,36,37]: (1) data pre-processing, (2) implementation of classification algorithms, (3) model validation and (4) evaluation of predictive performance (Fig. 1).

Data pre-processing

This step requires the treatment of missing variables and we decided to remove every row with unknown values. We substituted qualitative predictor variables by creating dummy variables, represented by binary values of 0 and 1. Also, we performed normalization and standardization processes for adjustments related to the scale of each variable.

We assessed the collinearity between predictors using Spearman's correlation test (the threshold for exclusion: $rho > 0.80$). Problems with the imbalance in the distribution of classes were solved by oversampling the minority class, where new instances were randomly produced by duplication, based on the input data, according to the methodology used by the Data Sampler function in the Orange software™ (version 3.29.3).

Classification Algorithms

We implemented Lasso penalized Logistic Regression (LR), Random forest (RF) and Extreme Gradiente Boosting (XGBoost). These are supervised learning algorithms often used to solve classification problems. All implementations were performed in Orange software™.

Data Partitioning

The final dataset consisted of 18 predictor variables and the outcome labels (presence (1) and absence (2) of depressive symptoms) that was partitioned into two data subsets for training and testing the models (Fig.1), 66% training data the 34% reserved to test the final performance of the algorithms and verify their respective generalization capacity after the insertion of new data.

Training and Validation

Validation with the training data was performed to adjust the combination of the best hyperparameters, necessary to control the complexity of the models (overfitting) and to optimize their performance, maintaining the balance between bias and variance. We used a 10-

fold cross-validation method (k-folds) to validate the predictive performance of our models (Fig. 1).

Predictive performance

To assess the predictive performance of each model, we used: Area Under the Curve (AUC), Accuracy (AC), Precision (PC), Sensitivity, Specificity, F1 Score, and Recall (RC). Furthermore, we created confusion matrices to estimate the performance of the classifiers considering the different classes, enabling us to extract the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV). The PPV was calculated as the number of cases that actually have depressive symptoms, divided by the number of cases that the model classifies as having this condition. The NPV was calculated as the number of cases that actually show the absence of depressive symptoms, divided by the number of cases that the classifier identifies as healthy. The percentage of the individual proportion of predicted classes was also verified.

Variable importance

To assess the importance of the predictors in the detection of depressive symptoms, the "information gain" of each respective variable was used as a parameter. Gain refers to the improvement of accuracy in a particular branch of the decision tree in which the variable in question is inserted.

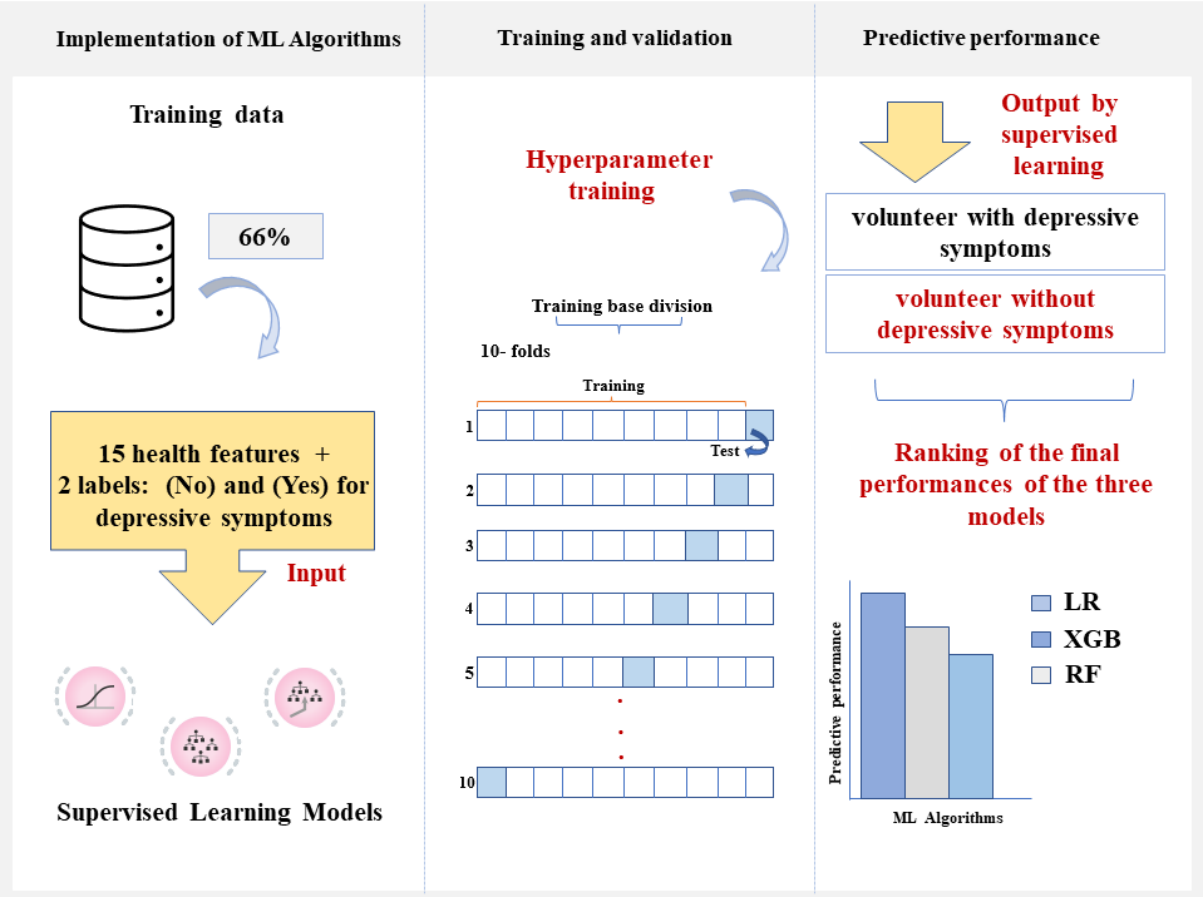

Figure 1 - Schematic representation of the methodology used to implement supervised machine learning models to predict depressive symptoms.

3. Results

Descriptive and inferential analysis of the eligible sample

Descriptive analysis

The sample consisted of 2,907 eligible participants, most of whom were women (51.5%) and with a mean age of 59.4 years. According to the PHQ-9 score, 25.1% were labelled with 'yes', representing the presence of depressive symptoms (Table 2). Additional information about the descriptive statistics of the other predictor variables can be accessed in tables 1 and 2.

Table 1 - Summary of descriptive statistics for all numerical predictors.

Feature	Mean	Median	Standard deviation
Age	59.4	59	11.9
Body Mass Index (kg/m²)	29.9	28.9	6.7
Total Cholesterol (mg/dl)	195	193	42.2
C-Reactive Protein (mg/l)	4.4	2.1	8.4
Glycohemoglobin (%)	6.06	5.7	1.2
High Density Lipoprotein (mg/dl)	54.6	51	18.2
Sedentary Activity (min.)	365	360	198
Sleep Duration (min.)	460	480	90.7
Sleep Onset (h)	22:45	22:30	118 min.
Sleep Offset (h)	06:01	06:00	155 min.
Waist Circumference (cm)	103	101	15.6
Weight (kg)	82.3	79.4	20.5

Table 2 - Absolute and relative frequency of levels referring to all predictive categorical variables and the target class of the prediction.

Name	Role	Levels	AF	RF(%)
Gender	feature	female	1497	51.5%
		male	1410	48.5%
Vigorous Recreational Activity	feature	no	2405	82.7%
		yes	502	17.3%
Moderate Recreational Activity	feature	no	1741	59.9%
		yes	1166	40.1%
Daytime Sleepiness	feature	sometimes	927	31.9%
		rarely	711	24.4%
		never	580	19.9%
		often	464	15.9%
		almost always	225	7.7%
Depressive symptoms	target	no	2176	74.9%

	yes	731	25.1%

Note. (FA)= Frequency Absolute and (FR)= Frequency Relative in percentage.

Inferential analysis

When considering the relationship between the PHQ-9 score and the quantitative predictor variables, a positive correlation was observed between the PHQ-9 score and BMI (rho = 0.137; $p < 0.05$), PHQ-9 score and WC (rho = 0.14; $p < 0.05$) and between PHQ-9 score and CRP (rho = 0.125; $p < 0.05$). The other variables showed a correlation coefficient below 0.1. Thus, these findings suggest a non-linear interaction between the predictor variables in question and the PHQ-9 score, which represents the severity of depressive symptoms (Appendix fig. 1).

We observed an association between depressive symptoms and daytime sleepiness ($X^2(4) = 279$; $p < 0.05$), vigorous recreational activity ($X^2(1) = 23.9$; $p < 0.05$), moderate recreational activity (X^2 (1) = 29.4; $p < 0.05$) and sex ($X^2(1) = 22.6$; $p < 0.05$), evidencing a relationship of dependence between the variables. According to the contingency table (Table S1), we observed more participants with depressive symptoms within the groups of individuals classified as experiencing daytime sleepiness (almost always or often) and more participants without depressive symptoms in the groups of individuals who never or rarely presented daytime sleepiness, when compared to the expected values. Still, in contrast to the expected values, we observed more men in the group of participants without depressive symptoms and more women in the group with such symptoms. For vigorous and moderate recreational activity, we observed more people who practiced these activities in the group of individuals classified with no symptoms and more participants who did not perform them in the group characterized with the presence of symptoms. Furthermore, participants who presented depressive symptoms spent more time in sedentary activities in relation to individuals without depressive symptoms (Table 3), 60 minutes longer (median=360 min) in relation to the group without depressive symptoms.

Depressive symptoms were also associated with sleep onset ($X^2(52) = 104$; $p < 0.05$) and sleep offset ($X^2(77) = 142$; $p < 0.05$). We observed a higher frequency of participants belonging to the group with symptoms initiating sleep later, as well as waking up later, in comparison with those without symptoms.

Table 3 - Differences between the medians of the characteristics of the groups, verified by the Kruskal-Wallis H test.

Characteristics	Group without depressive symptoms (median)	Group with depressive symptoms (median)	X^2	df	*p-value*
Age	59	59	0.006	1	0.938
BMI (kg/m²)	28.6	30.2	33.65	1	< .001
TC (mg/dl)	192	193	0.04	1	0.828
CRP (mg/l)	1.9	2.7	31.3	1	< .001
HbA1c (%)	5.7	5.8	17.9	1	< .001
HDL (mg/dl)	52	50	9.3	1	0.002
SA (min.)	300	360	9.13	1	0.003
SD (h)	7.5	8.	6.3	1	0.012
Sleep on. (min.)	1350	1350	5.5	1	0.018
Sleep off. (min.)	360	390	13.9	1	< .001
WC (cm)	100	104	33.5	1	< .001
Weight (kg)	78.6	81.7	11.2	1	< .001

Note. (BMI)- Body Mass Index; (TC)- Total cholesterol; (CRP)- C-Reactive Protein; (HbA1c)- Glycohemoglobin; (HDL)- High-Density Lipoprotein; (SA)- Sedentary Activity; (SD)- Sleep Duration; (Sleep on)- Sleep onset; (Sleep off)- Sleep offset and (WC)- Waist Circumference.

Regarding the biomarkers for obesity, BMI ($X^2(1)= 33.65$; $p<0.05$), CRP ($X^2(1)= 31.3$; $p<0.05$), WC ($X^2(1) = 33.5$; $p<0.05$), HDL ($X^2(1)= 9.3$; $p<0.05$) and Weight ($X^2(1)= 11.2$; $p<0.05$) differed significantly between groups (Table 3). No significant differences were observed in the serum total cholesterol level between the groups (Table 3).

Sleep habits also differed significantly between groups (Table 3). Individuals with depressive symptoms went to sleep 16 minutes earlier (10:57 pm, on average) and woke up 47 minutes later (at 6:11 am, on average). In addition, on average, the group with depressive symptoms slept 30 minutes longer than the volunteers without depressive symptoms.

Supervised machine learning in predicting depressive symptoms

Data pre-processing

After adjusting the imbalance between the target classes, the final sample number increased from 2907 to 3638 volunteers, with the insertion of new instances. The variables

related to anthropometric measurements (weight, BMI, and WC) were the only ones that showed a high correlation with each other, with *rho* above 0.8 (Figure S1). Among them, weight was excluded from the dataset, as studies indicate that both, general obesity (assessed by the BMI), and abdominal obesity (assessed by the WC), are the most important metrics, both having an important association with depressive symptoms in middle-aged adults and elderly [38]. Thus, the final dataset had 15 predictor variables, after filtering out highly correlated predictors (Table S2).

Definition of hyperparameters

Table 4 - Hyperparameter definition with 10-fold cross-validation.

Model	Hyperparameter	Fixed values (All features)
XGBoost	Maximum tree depth	6
	Boosting learning rate	0.3
	Number of trees	100
	Regularization strength	1
	Fraction of training instances	1
	Fraction of features for each tree	1
	Fraction of features for each level	1
	Fraction of features for each split	1
Random Forest	Number of trees	10
	Maximal number of considered features	7
	Maximal tree depth	18
	Stop splitting nodes with maximum instances	5
Logistic Regression	Regularization type	Lasso (L1)
	Regularization strength	1

Comparison of the three models

XGBoost was the one with the highest predictive performance, according to the main evaluation metrics (AUC=0.92; Accuracy=0.87 and Precision=0.87) (Table 5). Furthermore, this was the model that best managed to predict cases considered truly positive for depressive symptoms, with a PPV equal to 0.80, when compared to RF (0.77) and LR (0.64) (Table 4).

Moreover, XGBoost and Random Forest had similar proportions of correct answers in classifying cases for the presence of depressive symptoms, with 80.6% and 77%, respectively (Fig. 2).

Table 5 - Evaluation metrics.

Model	AUC	AC	PC	Recall	F1	PPV	NPV
XGBoost	0.92	0.87	0.87	0.87	0.87	0.80	0.92
Random Forest	0.89	0.82	0.83	0.82	0.83	0.77	0.87
Logistic Regression	0.71	0.67	0.67	0.67	0.66	0.64	0.68

Note. (AUC)- Area under the curve; (AC)- Accuracy; (PC)- Precision; (F1)- F1 Score; (PPV)- Positive Predictive Value and (NPV)- Negative Predictive Value.

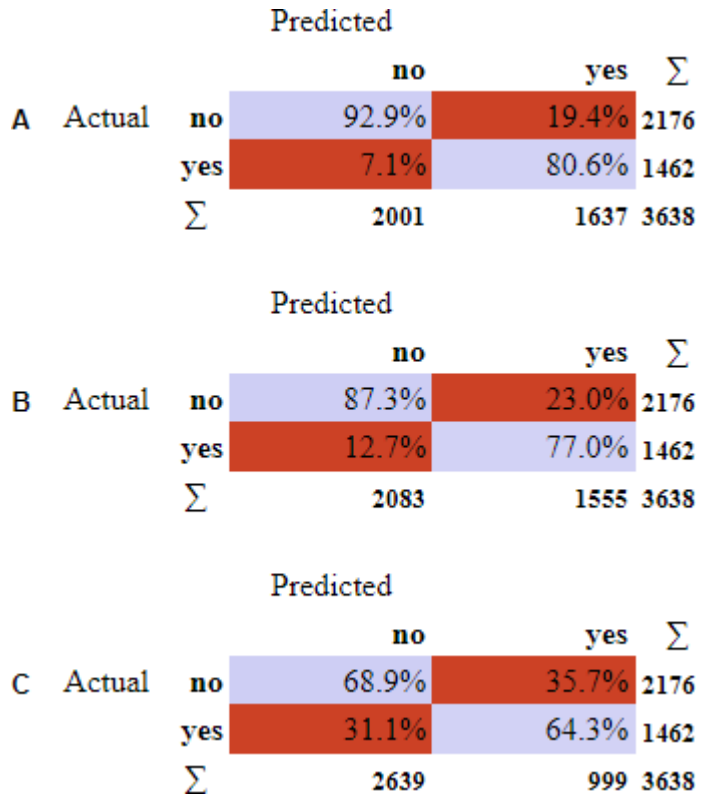

Figure 2 - Confusion matrix of tested models with the predicted proportion for each class. In **(a)**: XGBoosting; **(b)** Random Forest and **(c)** Logistic Regression.

Variable importance

The most significant predictive variable for depressive symptoms was daytime sleepiness when compared to the other features in descending order of importance (Table 6).

Table 6 - Importance of the variable according to information gain. (#)- stands for the number of levels of a given categorical variable.

Attributes	#	Information gain
Daytime Sleepiness	5	0.079
Waist Circumference		0.013
Body Mass Index		0.012
Sleep onset		0.011
Sleep offset		0.011
Sleep Duration		0.011
C-Reactive Protein		0.010
Moderate Recreational Activity	2	0.010
Vigorous Recreational Activity	2	0.008
Gender		0.007
Glycohemoglobin		0.006
High-Density Lipoprotein		0.004
Age		0.003
Sedentary Activity		0.003
Total Cholesterol		0.002

4. Discussion

Recently, machine learning has been successfully applied to predict depression, from the diagnosis to treatment response, through the use of multimodal wearable devices [39], 24-h locomotor activity data [40], and predictive features extracted from neuroimaging data [41]. However, none of these studies is solely based on ordinary, widely available clinical data.

Here, we revealed that excessive daytime sleepiness is the most important feature to predict the presence of depressive symptoms in middle-aged and elderly Americans. Community-based studies focused on the elderly population of different countries, which investigated the association or prevalence of EDS in depression, support our findings by showing a significant association between EDS, depressive symptoms, and the severity of depression [42]. Also, an increased risk of depression is related to daytime sleepiness compared to other sleep-wake disorders and medical conditions such as obesity and diabetes [43]. Furthermore, longitudinal research revealed that a decrease in depressive symptoms is one of the main predictors of remission of EDS [44].

EDS is characterized by the difficulty of maintaining wakefulness and alertness during the daytime, being a cause of traffic and workplace accidents, leading to damage to life and health [45]. It partially results from chronic sleep deprivation [46], unrested and insufficient [47]. Particularly in older adults, fragmented sleep, insomnia, obstructive sleep apnea and other sleep-related disorders also reduce total sleep time [48].

Chronic sleep deprivation affects the serotonergic system and the hypothalamic-pituitary-adrenal (HPA) axis responsible for the physiological response to stress, whose action causes changes in serotonin receptors (5-HT1A) and in the neuroendocrine response of adrenocorticotropic hormone (ACTH) and corticosterone (CORT) release [49]. These alterations are similar to the underlying neuronal processes of depression, which present hyperactivity of the HPA axis marked by the hypersecretion of ACTH and glucocorticoids [50] and a decrease in the availability of serotonin [51]. Animal model studies described that sleep deprivation for up to eight days causes gradual postsynaptic desensitization in the serotonin receptor (5-HT1A), and this persists even after sleep recovery [52]. Moreover, chronic sleep deprivation sensitized the HPA axis, resulting in elevated levels of ACTH and CORT after every 20-hour period of sleep deprivation for seven days [53].

When evaluating total self-reported sleep duration, we observed that individuals with symptoms of depression slept on average longer than those with no symptoms. Most studies, however, have reported a strong association between short sleep duration and depression [22], with participants suffering from depression reporting up to 40 minutes less sleep [54]. The association between the level of depressive symptoms and sleep duration in the elderly seems to be non-linear [55], although extremely short sleep duration (less than 4 hours of sleep) is associated with a higher risk of presenting symptoms of depression. Other studies including middle-aged and elderly participants, emphasized that short sleep duration is a risk factor for both incident and recurrent depression, with equal risk probability for both age groups [56]. On the other hand, long sleep duration (≥ 9) in the elderly is associated with EDS, which may reflect poor sleep quality in these individuals (57).

In addition to increased sleep duration in symptomatic participants, they also exhibited a delay in sleep onset and offset when compared with asymptomatic participants. This result is consistent with the literature and a typical finding in depression [58].

Higher BMI and WC were observed in our sample of individuals with depressive symptoms, compared to healthy volunteers, which is in accordance with the literature. American women have been reported to show a greater probability of the occurrence of depressive symptoms when their BMI is above 30kg/m². Moreover, a recent meta-analysis

study reported that volunteers with obesity are 1.18 times more likely to manifest depressive symptoms than those with a healthy weight range [59]. We also found lower levels of HDL in individuals with depressive symptoms compared to those without symptoms, despite being within the normal range for the age group. By contrast, there was no significant difference between groups in the levels of total cholesterol, with both having levels within the range considered normal. A growing body of evidence supports that low levels of HDL are associated with the occurrence of depressive symptoms [10,11]. Other studies have shown that reduced levels of total cholesterol are not associated with depression and more severe symptoms in the elderly [60,61]. However, there are studies showing, in both middle-aged and elderly men, an association between reduced levels of TC and depressive symptomatology, representing an increased risk of developing it [12,13].

Significant differences between groups were also observed in the level of C-reactive protein (CRP). Several studies have reported results supporting our findings by showing an association between increasing levels of plasma CRP with an increased risk of depression [62]. Moreover, higher levels of CRP have been significantly associated with greater severity of depressive symptoms [8]. However, it is important to emphasize that the mean CPR values verified in both groups in the present study suggest systemic inflammation, which demonstrates how the general population shows signs of inflammation.

Physical activities of a recreational nature, from moderate to vigorous intensity levels, were less frequent among subjects with depressive symptoms. Similar results were obtained in a study that sought to characterize groups with depression through cluster solutions, evidencing a propensity of depressive subjects to avoid moderate recreational activities [63]. There is evidence among middle-aged and older adults that recreational physical activities, both vigorous and moderate, contribute to a decrease in more severe depression [64]. For instance, physical activity is generally associated with a reduced proportion of subjects exceeding a PHQ-9 score > 10, which indicates greater severity of symptoms of depression [65]. These results are in line with expectations since it has been shown that depressive patients avoid recurrent practices of moderate to vigorous physical activities, dedicating less time to them when compared with subjects without depression [26]. This trend is even more frequent among older individuals, with a higher risk of low physical activity [66]. It can be explained mainly by limitations in mobility, pain, and discomfort. In addition, the association between low levels of physical activity and depression is also due to somatic conditions related to increased functional limitations, increased use of medication and psychosocial factors in individuals over 60 years of age [67].

Furthermore, sedentary behavior was prevalent in the group with symptoms of depression. These data corroborate results that show an association between depression and decreased minutes of physical activity [68]. Furthermore, even the chance of developing depression is increased by sedentarism [69].

Some important limitations in the present study are worth mentioning. For example, only weekday data for self-reported sleep onset, sleep offset and sleep duration data were available, which prevented us to analyse the instability in the sleep-wake behavior between weekdays and weekends. In addition, we did not have access to objective data, such as actigraphy, which would provide more accurate information about both the sleep-wake cycle and an estimate of the total time spent during the week in moderate to vigorous physical activity.

5. Conclusion

Sleep and physical activity features, in addition to classical biomarkers of obesity and diabetes, jointly assume significant importance to predict, with accuracy and precision of 87%, the occurrence of depressive symptoms in middle-aged and elderly individuals. Daytime sleepiness it the most important predictor of depressive symptoms, when compared to the other predictors used in this study. Individuals with depressive symptoms often experience excessive daytime sleepiness, tend to fall asleep and wake up later, have higher BMI and WC, have poorer glycemic control, and avoid moderate and vigorous recreational physical activity. Compared to psychometric analysis tools that require specialization and are time-consuming, machine learning predictive models facilitate the screening of depressive symptoms in elderly and middle-aged patients suffering from depression, minimizing morbidity and mortality through early treatment.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Stephania Ruth Basilio Silva Gomes: Contributed to the study design, formal data analysis, interpretation and writing of the manuscript. **Malcolm von Schantz:** Contributed to the writing and critical review of the manuscript. **Mario Leocadio-Miguel:** Contributed to the design and supervision of the study, in addition to the interpretation and writing of the manuscript.

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Supplementary material

Supplementary Table 1: Contingency table for different levels of categorical variables.

		Depressive Symptoms		
DS		**no**	**yes**	**Total**
almost always	Count	92	133	225
	Expected count	168	56.6	225
never	Count	502	78	580
	Expected count	434	145.8	580
often	Count	271	193	464
	Expected count	347	116.7	464
rarely	Count	595	116	711
	Expected count	532	178.8	711
sometimes	Count	716	211	927
	Expected count	694	233.1	927
Total	Count	2176	731	2907
	Expected count	2176	731	2907
MRA				
no	Count	1241	500	1741
	Expected count	1303	438	1741
yes	Count	935	231	1166
	Expected count	873	293	1166
Total	Count	2176	731	2907

	Expected count	2176	731	2907
VRA				
no	Count	1757	748	2405
	Expected count	1800	605	2405
yes	Count	419	83	502
	Expected count	376	126	502
Total	Count	2176	731	2907
	Expected count	2176	731	2907
Gender				
female	Count	1065	432	1497
	Expected count	1121	376	1497
male	Count	1111	299	1410
	Expected count	1055	355	1410
Total	Count	2176	731	2907
	Expected count	2176	731	2907

Note. (DS)- Daytime Sleepiness; (MRA)- Moderate Recreational Activity and (VRA)- Vigorous Recreational Activity.

Supplementary Table 2: List of 15 predictor variables selected in the final dataset

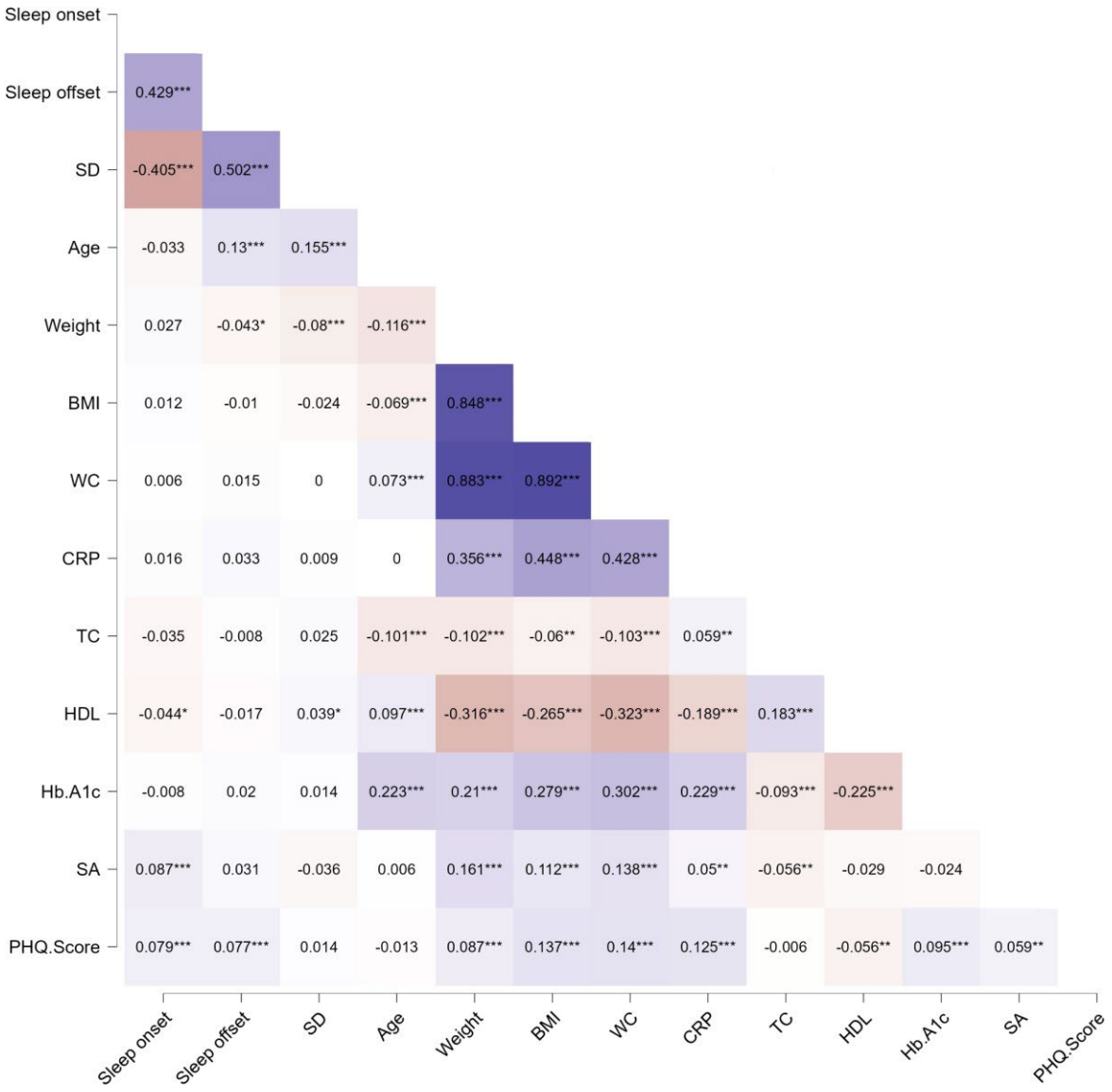
Attributes	Categories
Moderate Recreational Activity	Self-reported physical activity
Vigorous Recreational Activity	
Sedentary Activity	
Sleep onset	Self-reported sleep habits
Sleep offset	
Sleep duration	
Excessive daytime sleepiness	Indicative of sleep disturbance

Waist circumference	Anthropometric measurement
Body Mass Index	
C-reative protein	Plasma biomarkers of obesity
Total cholesterol	
High-density lipoprotein	
Glycated hemoglobin	Biomarker of diabetes
Sex	Sociodemographic characteristics
Age	

Supplementary Table 3: Glossary of key hyperparameters of machine learning models

XGBoost model specifications	**Maximum tree depth:** Specifies the maximum depth of the individual tree. **Boosting learning rate:** Specifies the boosting learning rate. The learning rate shrinks the contribution of each tree. **The number of trees:** Specifies how many gradient boosted trees will be included. A large number usually results in better performance. **Regularization strength:** Defines the cost strength of control over the model complexity to avoid overfitting. **Fraction of training instances:** Specifies the percentage of the training instances for fitting the individual tree. **Fraction of features for each tree:** Specifies the percentage of features to use when constructing each tree. **Fraction of features for each level:** Specifies the percentage of features to use for each level. **Fraction of features for each split:** Specifies the percentage of features to use for each split.

Random Forest model specifications	**Number of trees:** Specifies how many decision trees will be included in the forest. **Maximal number of considered features:** Number of attributes considered at each split. **Maximal tree depth:** The depth at which the trees will be grown. **Stop splitting nodes with maximum instances:** Specifies not to split subsets smaller than requested.
Logistic Regression Model Specifications	**Regularization type:** Regularization Lasso (L1). An alternative regularized version of the least squares method is Lasso (absolute minimum selection and shrinkage operator). **Regularization strength:** Sets the cost strength (default is C=1).



Supplementary Figure 1: Spearman's correlation between quantitative predictor variables and PHQ-9 score. (SD)- Sleep Duration; (BMI)- Body Mass Index; (WC)- Waist Circumference; (CRP)- C-Reactive Protein; (TC)- Total cholesterol; (HDL)- High Density Lipoprotein; (Hb. A1c)- Glycohemoglobin; (SA)- Sedentary Activity and (PHQ.Score)- PHQ-9 score. Note. * $p < .05$, ** $p < .01$, *** $p < .001$.

Predicting depressive symptoms in middle-aged and elderly adults using sleep data and clinical health markers: a machine learning approach

Stephania Ruth Basilio Silva Gomes [a], Malcolm von Schantz [b], Mario Leocadio-Miguel [a]

[a] Department of Physiology and Behavior, Federal University of Rio Grande Do Norte, Natal, Rio Grande do Norte, Brazil.

[b] Faculty of Health and Life Sciences, Northumbria University, Newcastle, UK.

*Corresponding author: mario.miguel@ufrn.br

CRediT authorship contribution statement

Stephania Ruth Basilio Silva Gomes: Contributed to the study design, formal data analysis, interpretation and writing of the manuscript. **Malcolm von Schantz:** Contributed to the writing and critical review of the manuscript. **Mario Leocadio-Miguel:** Contributed to the design and supervision of the study, in addition to the interpretation and writing of the manuscript.

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Stephania Ruth Basilio Silva Gomes [a], Malcolm von Schantz [b], Mario Leocadio-Miguel [a]

[a] Department of Physiology and Behavior, Federal University of Rio Grande Do Norte, Natal, Rio Grande do Norte, Brazil.

[b] Faculty of Health and Life Sciences, Northumbria University, Newcastle, UK.

*Corresponding author: mario.miguel@ufrn.br

Highlights

- Sleep data facilitates the prediction of depressive symptoms in middle-aged and older adults.
- Daytime sleepiness is an important predictor of depressive symptoms.
- XGBoost outperforms other machine learning (ML) models in the prediction of depressive symptoms.
- ML models to predict depressive symptoms facilitate the screening of depression.

Abstract

Objectives: Comorbid depression is a highly prevalent and debilitating condition in middle-aged and elderly adults, particularly when associated with obesity, diabetes, and sleep disturbances. In this context, there is a growing need to develop efficient screening methods for cases based on clinical health markers for these comorbidities and sleep data. Thus, our objective was to detect depressive symptoms in these subjects, considering general biomarkers of obesity and diabetes and variables related to sleep and physical exercise through a machine learning approach. **Methods:** We used the National Health and Nutrition Examination Survey (NHANES) 2015-2016 data. Eighteen variables on self-reported physical activity, self-reported sleep habits, sleep disturbance indicative, anthropometric measurements, sociodemographic characteristics and plasma biomarkers of obesity and diabetes were selected as predictors. A total of 2,907 middle-aged and elderly subjects were eligible for the study. Supervised learning algorithms such as Lasso penalized Logistic Regression (LR), Random Forest (RF) and

Extreme Gradient Boosting (XGBoost) were implemented. **Results:** XGBoost provided greater accuracy and precision (87%), with a proportion of hits in cases with depressive symptoms above 80%. In addition, daytime sleepiness was the most significant predictor variable for predicting depressive symptoms. **Conclusions:** Sleep and physical activity variables, in addition to obesity and diabetes biomarkers, together assume significant importance to predict, with accuracy and precision of 87%, the occurrence of depressive symptoms in middle-aged and elderly individuals.

Keywords: Depressive symptomatology; Cardiometabolic syndrome; Sleep variables.

Abbreviations

AC

Accuracy

AUC

Area under curve

ACTH

Adrenocorticotropic hormone

BMI

Body mass index

CRP

C-reactive protein

CORT

Corticosterone

EDS

Excessive daytime sleepiness

FA

Frequency absolute

FR

Frequency relative

GPAQ

Global physical activity questionnaire

HPA

Hypothalamic-pituitary-adrenal

HDL

High-density lipoprotein

Hb A1c

Glycated hemoglobin

LR

Logistic regression

MDD

Major depressive disorders

ML

Machine learning

NPV

Negative predictive value

NHANES

National Health and Nutrition Examination Survey

NCHS

National Center for Health Statistic

PC

Precision

PA

Physical activity

PHQ-9

Patient health questionnaire

PPV

Positive predictive value

RF

Random forest

SA

Sedentary activity

SD

Sleep duration

TC

Total cholesterol

XGBoost

Extreme gradient boosting

5-HT1A

Serotonin receptors

1. Introduction

Depression is one of the most prevalent mental disorders, affecting a third of a billion people in the world [1]. Importantly, the prevalence of depressive symptoms in middle-aged and elderly adults is high, affecting their quality of life and increasing healthcare spending [2]. The coexistence of multiple comorbidities is common among older adults and there is evidence of a bidirectional association between multimorbidity and depression. For example, the prevalence of depression increases by 37.97% in elderly and middle-aged individuals facing more than three chronic conditions when compared to healthy volunteers [3].

Obesity is an example of a chronic condition that not only shares a common biological mechanism, but also displays a bidirectional relationship with depression, particularly in women [4]. Anthropometric measurements, such as the Body Mass Index (BMI) and the Waist Circumference (WC), are widely adopted to assess general and abdominal obesity, respectively. Both BMI and WC are increased in subjects presenting depressive symptoms when compared to healthy individuals [5]. C-Reactive Protein (CRP), an indicator of peripheral inflammatory processes, is also an indirect marker of obesity with the potential to predict depression. CRP serum concentration is higher in both obese and depressed individuals [6]. Moreover, in a predictive scenario, CRP can differentiate cases of unipolar and bipolar depression [7]. Furthermore, higher levels of CRP are significantly associated with the severity of depression in women [8].

In addition, the lipid profile, represented by high concentrations of total serum cholesterol (TC) and reduced levels of high-density lipoprotein (HDL), is an important marker of obesity in the metabolic syndrome, associated with a higher risk of developing cardiovascular diseases [9]. The same pattern in HDL levels was associated with long-term depression and long-term depressive symptomatology [10,11]. However, reduced levels of TC are associated with depressive symptoms, especially in middle-aged and elderly men [12,13].

Again, when considering the multicomorbid nature of the depressive disorder, researchers have shown that diabetes is also an important risk factor for the development of depression [14]. Moreover, an improvement in glycemic control from 10% to 25% is associated with a decrease in the prevalence of depression [15]. Finally, the elevation of glycated hemoglobin (HbA1c), frequently used as a biomarker of diabetes and pre-diabetes, also predicts depression [16].

Delayed sleep phase [17], instability in sleep onset and/or offset [18], and reduction of the amplitude of multiple circadian rhythms [19,20] are related to depression. In addition, individuals experiencing depression are also often concurrently affected by sleep disorders, such as excessive daytime sleepiness (EDS), which appears to be a common symptom of depression [21]. Interestingly, however, the reduction in nocturnal sleep duration, which is usually associated with EDS, seems to be irrelevant to predicting depression. However, a recent meta-analysis showed that short sleep duration, per se, is associated with the risk of depression [22]. Furthermore, reduced mean sleep duration can predict an increase in depressive symptoms when presented over a period of at least two weeks [23].

Importantly, EDS and insufficient sleep duration result in increased sedentary behavior and reduced physical activity (PA) levels. PA levels are reduced as a function of sleep duration

in subjects with EDS [24]. Furthermore, a more sedentary lifestyle is associated with a higher risk of developing major depressive disorder (MDD) and this relationship is mediated by sleep disorders in general [25]. In addition, subjects with depression tend to perform recreational physical activities less frequently and spend less time on moderate to vigorous activities [26].

Given the increasing difficulty and importance of detecting depression, particularly in middle-aged adults and the elderly, fast and accurate screening methods are needed [27]. Depression screening is usually based on questionnaires and self-report scales, covering questions about sociodemographic characteristics, risk factors and comorbid medical conditions associated with depression [28]. Moreover, interpretation issues and the lack of more objective clinical data may explain the low detection rate of depression found in primary care settings, for example [29]. In this scenario, the application of state of art statistics based on artificial intelligence, such as machine learning (ML), promises to revolutionize clinical practice in psychiatry by enabling the differential diagnosis of depression based on objective, ordinary clinical data [30]. Rather than solving inference problems and understanding the relationship between variables, ML algorithms can learn directly from data and search for complex, non-linear, patterns to enable prediction [31].

Therefore, the objective of the study was to predict the occurrence of depressive symptoms in middle-aged and elderly adults through sleep-related variables, levels of physical activity, anthropometric measures, obesity, and diabetes biomarkers, using a machine learning approach (ML). In addition, we aim to evaluate the potential of multiple predictive variables, together and individually, in predicting the occurrence of depressive symptoms.

2. Methods

Database

Data was retrieved from the National Health and Nutrition Examination Survey (NHANES), biennial period (2015-2016). NHANES is a study program of the National Center for Health Statistics (NCHS) aimed at assessing the health and nutritional status of individuals in the United States, compiling data from a combination of questionnaires and clinical examinations, supporting researchers around the world with an interest in epidemiological studies and aimed at understanding public health problems [32].

Eligible Sample

A total of 2,907 middle-aged and elderly subjects, participants of NHANES (2015-2016), with and without depressive symptoms, were eligible for and included in the present study.

Measures of depressive symptoms

To assess the occurrence of depressive symptoms, we extracted responses from the Patient Health Questionnaire (PHQ-9). This instrument delimits different cut-off points to classify the degree of severity of depressive symptoms into different levels: no depression (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27) [33]. In the study, two cut-off points were determined to classify individuals according to the absence or presence of depressive symptoms. Thus, the established scoring ranges were 0-4 and 5-27, respectively.

Selection of predictor variables (features)

The variable selection was guided by the literature review of depression and its comorbidities. In total, 18 variables were selected, distributed into 7 distinct resource axes: (1) self-reported physical activity (the occurrence of moderate or vigorous recreational activities and sedentary activity (SA)), (2) self-reported sleep habits (sleep onset, sleep offset and sleep duration (SD)), (3) indicative of sleep disturbance (excessive daytime sleepiness), (4) anthropometric measurements (weight, WC and BMI), (5) plasma biomarkers of obesity (C-reactive protein (CRP), total cholesterol (TC) and high-density lipoprotein (HDL), (6) biomarker of diabetes (glycated hemoglobin (HbA1c) and (7) sociodemographic characteristics (sex and age).

Measures of predictor variables

The GPAQ - Global Physical Activity Questionnaire [34] provided data on the prevalence of physical activity in the recreational context, from moderate to vigorous level (at least 10 minutes in a typical week), as well as the time allocated in sedentary activities on a normal day, especially sitting and resting.

The assessment of sleep habits and EDS was established through general self-report questionnaires. Participants reported their usual bedtime, wake-up time and sleep duration on weekdays and workdays. EDS was based on the volunteer's perception of the frequency of diurnal excessive sleepiness in the last 30 days. Through a reference scale the EDS was

classified as: never, rarely (once a month), sometimes (2-4 times a month), often (5-15 times a month) and almost always (16-30 times a month).

Data on the age and sex of participants were acquired from a sociodemographic survey. The anthropometric variables included weight (kg), waist circumference (cm) and BMI (kg/m^2).

To assess plasma biomarkers, such as high-sensitivity CRP, CT and HDL, minimum blood detection limits were determined: 0.11 mg/l, 3mg/dl and 4mg/dl, respectively. Glycated hemoglobin data was obtained from accurate measurements of its stable form (HbA1c) in relative percentages. More details on data collection and processing can be found in the NHANES website (https://www.cdc.gov/nchs/nhanes).

Descriptive and inferential analysis of the eligible sample

Data were submitted to a descriptive statistical routine, considering measures of central tendency (mean and median) and standard deviation for quantitative variables. Furthermore, the normality of these features was verified using the Shapiro-Wilk test. Absolute and relative frequencies for all levels of nominal categorical predictor variables were calculated, as well as for the binary target class of prediction.

Spearman's correlation test was applied to assess the existence of a linear association between predictor variables related to sleep habits, anthropometric measurements, obesity/diabetes plasma biomarkers, in addition to age and the level of depressive symptoms. To investigate whether the groups of participants with and without depressive symptoms differ in terms of the frequency of daytime sleepiness, physical activity at different levels in a recreational context, and gender, the chi-square test of association (independence) was used and the frequency of observed and expected participants at each attribute level was calculated, assuming independence between these variables. In addition, the same test was used to compare possible differences in sleep onset and sleep offset time frequencies between the groups.

To assess whether individuals with and without depressive symptoms vary in terms of age, BMI, TC, CRP, HbA1c, HDL, SA, SD, sleep onset, sleep offset, WC and weight, the Kruskal-Wallis H test was applied.

Supervised machine learning in predicting depressive symptoms

To predict the occurrence of depressive symptoms, based on the predictive features, we developed different supervised machine learning models following four steps [35,36,37]: (1) data pre-processing, (2) implementation of classification algorithms, (3) model validation and (4) evaluation of predictive performance (Fig. 1).

Data pre-processing

This step requires the treatment of missing variables and we decided to remove every row with unknown values. We substituted qualitative predictor variables by creating dummy variables, represented by binary values of 0 and 1. Also, we performed normalization and standardization processes for adjustments related to the scale of each variable.

We assessed the collinearity between predictors using Spearman's correlation test (the threshold for exclusion: $rho > 0.80$). Problems with the imbalance in the distribution of classes were solved by oversampling the minority class, where new instances were randomly produced by duplication, based on the input data, according to the methodology used by the Data Sampler function in the Orange software™ (version 3.29.3).

Classification Algorithms

We implemented Lasso penalized Logistic Regression (LR), Random forest (RF) and Extreme Gradiente Boosting (XGBoost). These are supervised learning algorithms often used to solve classification problems. All implementations were performed in Orange software™.

Data Partitioning

The final dataset consisted of 18 predictor variables and the outcome labels (presence (1) and absence (2) of depressive symptoms) that was partitioned into two data subsets for training and testing the models (Fig.1), 66% training data the 34% reserved to test the final performance of the algorithms and verify their respective generalization capacity after the insertion of new data.

Training and Validation

Validation with the training data was performed to adjust the combination of the best hyperparameters, necessary to control the complexity of the models (overfitting) and to optimize their performance, maintaining the balance between bias and variance. We used a 10-

fold cross-validation method (k-folds) to validate the predictive performance of our models (Fig. 1).

Predictive performance

To assess the predictive performance of each model, we used: Area Under the Curve (AUC), Accuracy (AC), Precision (PC), Sensitivity, Specificity, F1 Score, and Recall (RC). Furthermore, we created confusion matrices to estimate the performance of the classifiers considering the different classes, enabling us to extract the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV). The PPV was calculated as the number of cases that actually have depressive symptoms, divided by the number of cases that the model classifies as having this condition. The NPV was calculated as the number of cases that actually show the absence of depressive symptoms, divided by the number of cases that the classifier identifies as healthy. The percentage of the individual proportion of predicted classes was also verified.

Variable importance

To assess the importance of the predictors in the detection of depressive symptoms, the "information gain" of each respective variable was used as a parameter. Gain refers to the improvement of accuracy in a particular branch of the decision tree in which the variable in question is inserted.

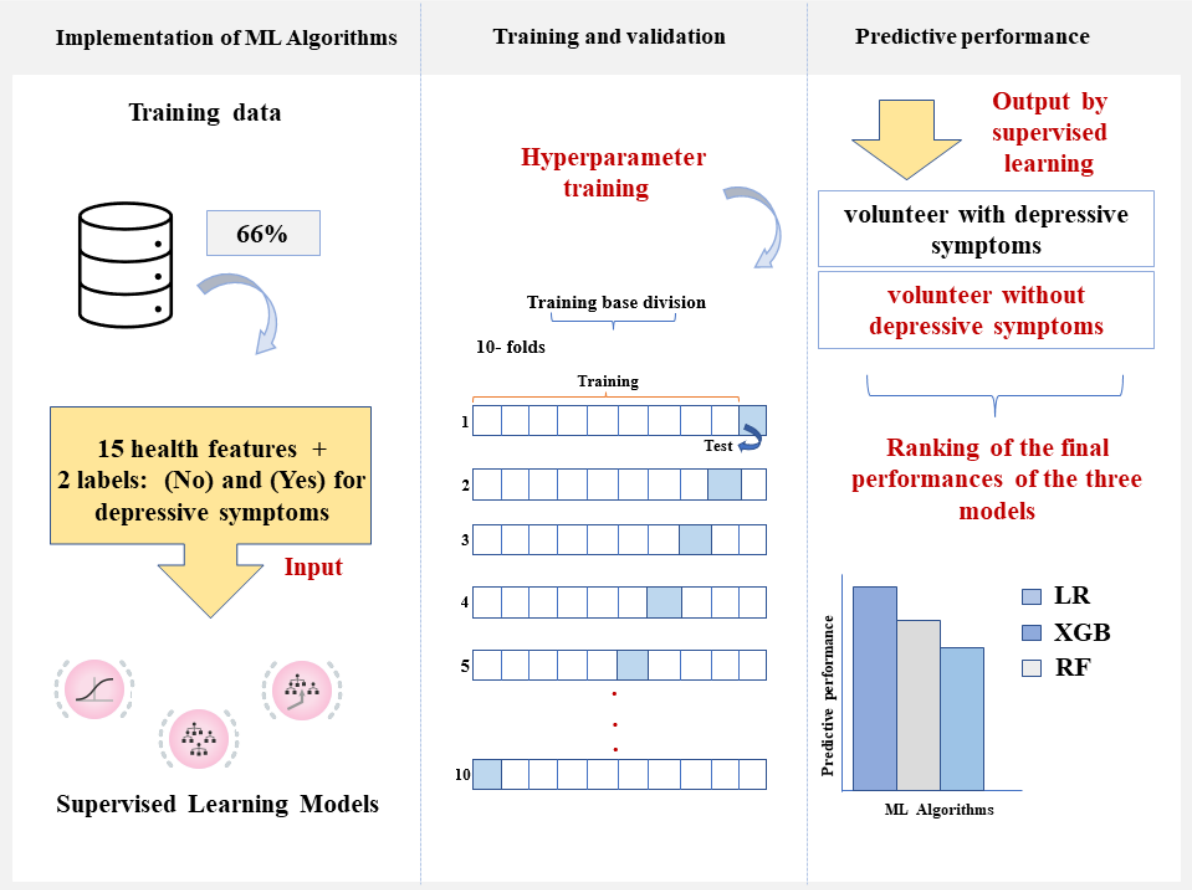

Figure 1 - Schematic representation of the methodology used to implement supervised machine learning models to predict depressive symptoms.

3. Results

Descriptive and inferential analysis of the eligible sample

Descriptive analysis

The sample consisted of 2,907 eligible participants, most of whom were women (51.5%) and with a mean age of 59.4 years. According to the PHQ-9 score, 25.1% were labelled with 'yes', representing the presence of depressive symptoms (Table 2). Additional information about the descriptive statistics of the other predictor variables can be accessed in tables 1 and 2.

Table 1 - Summary of descriptive statistics for all numerical predictors.

Feature	Mean	Median	Standard deviation
Age	59.4	59	11.9
Body Mass Index (kg/m²)	29.9	28.9	6.7
Total Cholesterol (mg/dl)	195	193	42.2
C-Reactive Protein (mg/l)	4.4	2.1	8.4
Glycohemoglobin (%)	6.06	5.7	1.2
High Density Lipoprotein (mg/dl)	54.6	51	18.2
Sedentary Activity (min.)	365	360	198
Sleep Duration (min.)	460	480	90.7
Sleep Onset (h)	22:45	22:30	118 min.
Sleep Offset (h)	06:01	06:00	155 min.
Waist Circumference (cm)	103	101	15.6
Weight (kg)	82.3	79.4	20.5

Table 2 - Absolute and relative frequency of levels referring to all predictive categorical variables and the target class of the prediction.

Name	Role	Levels	AF	RF(%)
Gender	feature	female	1497	51.5%
		male	1410	48.5%
Vigorous Recreational Activity	feature	no	2405	82.7%
		yes	502	17.3%
Moderate Recreational Activity	feature	no	1741	59.9%
		yes	1166	40.1%
Daytime Sleepiness	feature	sometimes	927	31.9%
		rarely	711	24.4%
		never	580	19.9%
		often	464	15.9%
		almost always	225	7.7%
Depressive symptoms	target	no	2176	74.9%

	yes	731	25.1%

Note. (FA)= Frequency Absolute and (FR)= Frequency Relative in percentage.

Inferential analysis

When considering the relationship between the PHQ-9 score and the quantitative predictor variables, a positive correlation was observed between the PHQ-9 score and BMI (rho = 0.137; $p < 0.05$), PHQ-9 score and WC (rho = 0.14; $p < 0.05$) and between PHQ-9 score and CRP (rho = 0.125; $p < 0.05$). The other variables showed a correlation coefficient below 0.1. Thus, these findings suggest a non-linear interaction between the predictor variables in question and the PHQ-9 score, which represents the severity of depressive symptoms (Appendix fig. 1).

We observed an association between depressive symptoms and daytime sleepiness ($X^2(4) = 279$; $p < 0.05$), vigorous recreational activity ($X^2(1) = 23.9$; $p < 0.05$), moderate recreational activity (X^2 (1) = 29.4; $p < 0.05$) and sex ($X^2(1) = 22.6$; $p < 0.05$), evidencing a relationship of dependence between the variables. According to the contingency table (Table S1), we observed more participants with depressive symptoms within the groups of individuals classified as experiencing daytime sleepiness (almost always or often) and more participants without depressive symptoms in the groups of individuals who never or rarely presented daytime sleepiness, when compared to the expected values. Still, in contrast to the expected values, we observed more men in the group of participants without depressive symptoms and more women in the group with such symptoms. For vigorous and moderate recreational activity, we observed more people who practiced these activities in the group of individuals classified with no symptoms and more participants who did not perform them in the group characterized with the presence of symptoms. Furthermore, participants who presented depressive symptoms spent more time in sedentary activities in relation to individuals without depressive symptoms (Table 3), 60 minutes longer (median=360 min) in relation to the group without depressive symptoms.

Depressive symptoms were also associated with sleep onset ($X^2(52) = 104$; $p < 0.05$) and sleep offset ($X^2(77) = 142$; $p < 0.05$). We observed a higher frequency of participants belonging to the group with symptoms initiating sleep later, as well as waking up later, in comparison with those without symptoms.

Table 3 - Differences between the medians of the characteristics of the groups, verified by the Kruskal-Wallis H test.

Characteristics	Group without depressive symptoms (median)	Group with depressive symptoms (median)	X^2	df	*p-value*
Age	59	59	0.006	1	0.938
BMI (kg/m²)	28.6	30.2	33.65	1	< .001
TC (mg/dl)	192	193	0.04	1	0.828
CRP (mg/l)	1.9	2.7	31.3	1	< .001
HbA1c (%)	5.7	5.8	17.9	1	< .001
HDL (mg/dl)	52	50	9.3	1	0.002
SA (min.)	300	360	9.13	1	0.003
SD (h)	7.5	8.	6.3	1	0.012
Sleep on. (min.)	1350	1350	5.5	1	0.018
Sleep off. (min.)	360	390	13.9	1	< .001
WC (cm)	100	104	33.5	1	< .001
Weight (kg)	78.6	81.7	11.2	1	< .001

Note. (BMI)- Body Mass Index; (TC)- Total cholesterol; (CRP)- C-Reactive Protein; (HbA1c)- Glycohemoglobin; (HDL)- High-Density Lipoprotein; (SA)- Sedentary Activity; (SD)- Sleep Duration; (Sleep on)- Sleep onset; (Sleep off)- Sleep offset and (WC)- Waist Circumference.

Regarding the biomarkers for obesity, BMI ($X^2(1)= 33.65$; $p<0.05$), CRP ($X^2(1)= 31.3$; $p<0.05$), WC ($X^2(1) = 33.5$; $p<0.05$), HDL ($X^2(1)= 9.3$; $p<0.05$) and Weight ($X^2(1)= 11.2$; $p<0.05$) differed significantly between groups (Table 3). No significant differences were observed in the serum total cholesterol level between the groups (Table 3).

Sleep habits also differed significantly between groups (Table 3). Individuals with depressive symptoms went to sleep 16 minutes earlier (10:57 pm, on average) and woke up 47 minutes later (at 6:11 am, on average). In addition, on average, the group with depressive symptoms slept 30 minutes longer than the volunteers without depressive symptoms.

Supervised machine learning in predicting depressive symptoms

Data pre-processing

After adjusting the imbalance between the target classes, the final sample number increased from 2907 to 3638 volunteers, with the insertion of new instances. The variables

related to anthropometric measurements (weight, BMI, and WC) were the only ones that showed a high correlation with each other, with *rho* above 0.8 (Figure S1). Among them, weight was excluded from the dataset, as studies indicate that both, general obesity (assessed by the BMI), and abdominal obesity (assessed by the WC), are the most important metrics, both having an important association with depressive symptoms in middle-aged adults and elderly [38]. Thus, the final dataset had 15 predictor variables, after filtering out highly correlated predictors (Table S2).

Definition of hyperparameters

Table 4 - Hyperparameter definition with 10-fold cross-validation.

Model	Hyperparameter	Fixed values (All features)
XGBoost	Maximum tree depth	6
	Boosting learning rate	0.3
	Number of trees	100
	Regularization strength	1
	Fraction of training instances	1
	Fraction of features for each tree	1
	Fraction of features for each level	1
	Fraction of features for each split	1
Random Forest	Number of trees	10
	Maximal number of considered features	7
	Maximal tree depth	18
	Stop splitting nodes with maximum instances	5
Logistic Regression	Regularization type	Lasso (L1)
	Regularization strength	1

Comparison of the three models

XGBoost was the one with the highest predictive performance, according to the main evaluation metrics (AUC=0.92; Accuracy=0.87 and Precision=0.87) (Table 5). Furthermore, this was the model that best managed to predict cases considered truly positive for depressive symptoms, with a PPV equal to 0.80, when compared to RF (0.77) and LR (0.64) (Table 4).

Moreover, XGBoost and Random Forest had similar proportions of correct answers in classifying cases for the presence of depressive symptoms, with 80.6% and 77%, respectively (Fig. 2).

Table 5 - Evaluation metrics.

Model	AUC	AC	PC	Recall	F1	PPV	NPV
XGBoost	0.92	0.87	0.87	0.87	0.87	0.80	0.92
Random Forest	0.89	0.82	0.83	0.82	0.83	0.77	0.87
Logistic Regression	0.71	0.67	0.67	0.67	0.66	0.64	0.68

Note. (AUC)- Area under the curve; (AC)- Accuracy; (PC)- Precision; (F1)- F1 Score; (PPV)- Positive Predictive Value and (NPV)- Negative Predictive Value.

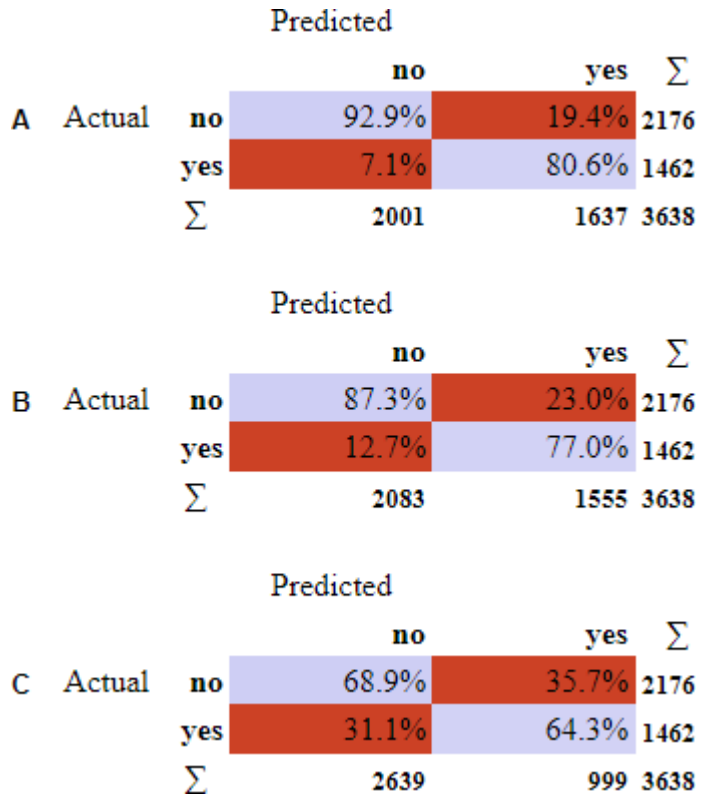

Figure 2 - Confusion matrix of tested models with the predicted proportion for each class. In **(a)**: XGBoosting; **(b)** Random Forest and **(c)** Logistic Regression.

Variable importance

The most significant predictive variable for depressive symptoms was daytime sleepiness when compared to the other features in descending order of importance (Table 6).

Table 6 - Importance of the variable according to information gain. (#)- stands for the number of levels of a given categorical variable.

Attributes	#	Information gain
Daytime Sleepiness	5	0.079
Waist Circumference		0.013
Body Mass Index		0.012
Sleep onset		0.011
Sleep offset		0.011
Sleep Duration		0.011
C-Reactive Protein		0.010
Moderate Recreational Activity	2	0.010
Vigorous Recreational Activity	2	0.008
Gender		0.007
Glycohemoglobin		0.006
High-Density Lipoprotein		0.004
Age		0.003
Sedentary Activity		0.003
Total Cholesterol		0.002

4. Discussion

Recently, machine learning has been successfully applied to predict depression, from the diagnosis to treatment response, through the use of multimodal wearable devices [39], 24-h locomotor activity data [40], and predictive features extracted from neuroimaging data [41]. However, none of these studies is solely based on ordinary, widely available clinical data.

Here, we revealed that excessive daytime sleepiness is the most important feature to predict the presence of depressive symptoms in middle-aged and elderly Americans. Community-based studies focused on the elderly population of different countries, which investigated the association or prevalence of EDS in depression, support our findings by showing a significant association between EDS, depressive symptoms, and the severity of depression [42]. Also, an increased risk of depression is related to daytime sleepiness compared to other sleep-wake disorders and medical conditions such as obesity and diabetes [43]. Furthermore, longitudinal research revealed that a decrease in depressive symptoms is one of the main predictors of remission of EDS [44].

EDS is characterized by the difficulty of maintaining wakefulness and alertness during the daytime, being a cause of traffic and workplace accidents, leading to damage to life and health [45]. It partially results from chronic sleep deprivation [46], unrested and insufficient [47]. Particularly in older adults, fragmented sleep, insomnia, obstructive sleep apnea and other sleep-related disorders also reduce total sleep time [48].

Chronic sleep deprivation affects the serotonergic system and the hypothalamic-pituitary-adrenal (HPA) axis responsible for the physiological response to stress, whose action causes changes in serotonin receptors (5-HT1A) and in the neuroendocrine response of adrenocorticotropic hormone (ACTH) and corticosterone (CORT) release [49]. These alterations are similar to the underlying neuronal processes of depression, which present hyperactivity of the HPA axis marked by the hypersecretion of ACTH and glucocorticoids [50] and a decrease in the availability of serotonin [51]. Animal model studies described that sleep deprivation for up to eight days causes gradual postsynaptic desensitization in the serotonin receptor (5-HT1A), and this persists even after sleep recovery [52]. Moreover, chronic sleep deprivation sensitized the HPA axis, resulting in elevated levels of ACTH and CORT after every 20-hour period of sleep deprivation for seven days [53].

When evaluating total self-reported sleep duration, we observed that individuals with symptoms of depression slept on average longer than those with no symptoms. Most studies, however, have reported a strong association between short sleep duration and depression [22], with participants suffering from depression reporting up to 40 minutes less sleep [54]. The association between the level of depressive symptoms and sleep duration in the elderly seems to be non-linear [55], although extremely short sleep duration (less than 4 hours of sleep) is associated with a higher risk of presenting symptoms of depression. Other studies including middle-aged and elderly participants, emphasized that short sleep duration is a risk factor for both incident and recurrent depression, with equal risk probability for both age groups [56]. On the other hand, long sleep duration (≥ 9) in the elderly is associated with EDS, which may reflect poor sleep quality in these individuals (57).

In addition to increased sleep duration in symptomatic participants, they also exhibited a delay in sleep onset and offset when compared with asymptomatic participants. This result is consistent with the literature and a typical finding in depression [58].

Higher BMI and WC were observed in our sample of individuals with depressive symptoms, compared to healthy volunteers, which is in accordance with the literature. American women have been reported to show a greater probability of the occurrence of depressive symptoms when their BMI is above 30kg/m². Moreover, a recent meta-analysis

study reported that volunteers with obesity are 1.18 times more likely to manifest depressive symptoms than those with a healthy weight range [59]. We also found lower levels of HDL in individuals with depressive symptoms compared to those without symptoms, despite being within the normal range for the age group. By contrast, there was no significant difference between groups in the levels of total cholesterol, with both having levels within the range considered normal. A growing body of evidence supports that low levels of HDL are associated with the occurrence of depressive symptoms [10,11]. Other studies have shown that reduced levels of total cholesterol are not associated with depression and more severe symptoms in the elderly [60,61]. However, there are studies showing, in both middle-aged and elderly men, an association between reduced levels of TC and depressive symptomatology, representing an increased risk of developing it [12,13].

Significant differences between groups were also observed in the level of C-reactive protein (CRP). Several studies have reported results supporting our findings by showing an association between increasing levels of plasma CRP with an increased risk of depression [62]. Moreover, higher levels of CRP have been significantly associated with greater severity of depressive symptoms [8]. However, it is important to emphasize that the mean CPR values verified in both groups in the present study suggest systemic inflammation, which demonstrates how the general population shows signs of inflammation.

Physical activities of a recreational nature, from moderate to vigorous intensity levels, were less frequent among subjects with depressive symptoms. Similar results were obtained in a study that sought to characterize groups with depression through cluster solutions, evidencing a propensity of depressive subjects to avoid moderate recreational activities [63]. There is evidence among middle-aged and older adults that recreational physical activities, both vigorous and moderate, contribute to a decrease in more severe depression [64]. For instance, physical activity is generally associated with a reduced proportion of subjects exceeding a PHQ-9 score > 10, which indicates greater severity of symptoms of depression [65]. These results are in line with expectations since it has been shown that depressive patients avoid recurrent practices of moderate to vigorous physical activities, dedicating less time to them when compared with subjects without depression [26]. This trend is even more frequent among older individuals, with a higher risk of low physical activity [66]. It can be explained mainly by limitations in mobility, pain, and discomfort. In addition, the association between low levels of physical activity and depression is also due to somatic conditions related to increased functional limitations, increased use of medication and psychosocial factors in individuals over 60 years of age [67].

Furthermore, sedentary behavior was prevalent in the group with symptoms of depression. These data corroborate results that show an association between depression and decreased minutes of physical activity [68]. Furthermore, even the chance of developing depression is increased by sedentarism [69].

Some important limitations in the present study are worth mentioning. For example, only weekday data for self-reported sleep onset, sleep offset and sleep duration data were available, which prevented us to analyse the instability in the sleep-wake behavior between weekdays and weekends. In addition, we did not have access to objective data, such as actigraphy, which would provide more accurate information about both the sleep-wake cycle and an estimate of the total time spent during the week in moderate to vigorous physical activity. Moreover, sleep data was obtained only from questionnaires, without specific and objective assessment of sleep efficiency and sleep quality, which may have also affected the associations. Finally, even though NHANES uses a multistage, stratified design, to produce a representative sample of the civilian resident population in the Unites States of America, causality or the direction of the relationships are limited due to its cross-sectional study design. the models developed in this research cannot be applied to other countries with different cultures and ancestralities. However, our model is important as a starting point for researchers in developing specific algorithms for particular situations.

5. Conclusion

Sleep and physical activity features, in addition to classical biomarkers of obesity and diabetes, jointly assume significant importance to predict, with accuracy and precision of 87%, the occurrence of depressive symptoms in middle-aged and elderly individuals. Daytime sleepiness it the most important predictor of depressive symptoms, when compared to the other predictors used in this study. Individuals with depressive symptoms often experience excessive daytime sleepiness, tend to fall asleep and wake up later, have higher BMI and WC, have poorer glycemic control, and avoid moderate and vigorous recreational physical activity. Compared to psychometric analysis tools that require specialization and are time-consuming, machine learning predictive models facilitate the screening of depressive symptoms in elderly and middle-aged patients suffering from depression, minimizing morbidity and mortality through early treatment.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Stephania Ruth Basilio Silva Gomes: Contributed to the study design, formal data analysis, interpretation and writing of the manuscript. **Malcolm von Schantz:** Contributed to the writing and critical review of the manuscript. **Mario Leocadio-Miguel:** Contributed to the design and supervision of the study, in addition to the interpretation and writing of the manuscript.

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Supplementary material

Supplementary Table 1: Contingency table for different levels of categorical variables.

DS		Depressive Symptoms		Total
		no	yes	
almost always	Count	92	133	225
	Expected count	168	56.6	225
never	Count	502	78	580
	Expected count	434	145.8	580
often	Count	271	193	464
	Expected count	347	116.7	464
rarely	Count	595	116	711
	Expected count	532	178.8	711
sometimes	Count	716	211	927

	Expected count	694	233.1	927
Total	Count	2176	731	2907
	Expected count	2176	731	2907
MRA				
no	Count	1241	500	1741
	Expected count	1303	438	1741
yes	Count	935	231	1166
	Expected count	873	293	1166
Total	Count	2176	731	2907
	Expected count	2176	731	2907
VRA				
no	Count	1757	748	2405
	Expected count	1800	605	2405
yes	Count	419	83	502
	Expected count	376	126	502
Total	Count	2176	731	2907
	Expected count	2176	731	2907
Gender				
female	Count	1065	432	1497
	Expected count	1121	376	1497
male	Count	1111	299	1410
	Expected count	1055	355	1410
Total	Count	2176	731	2907
	Expected count	2176	731	2907

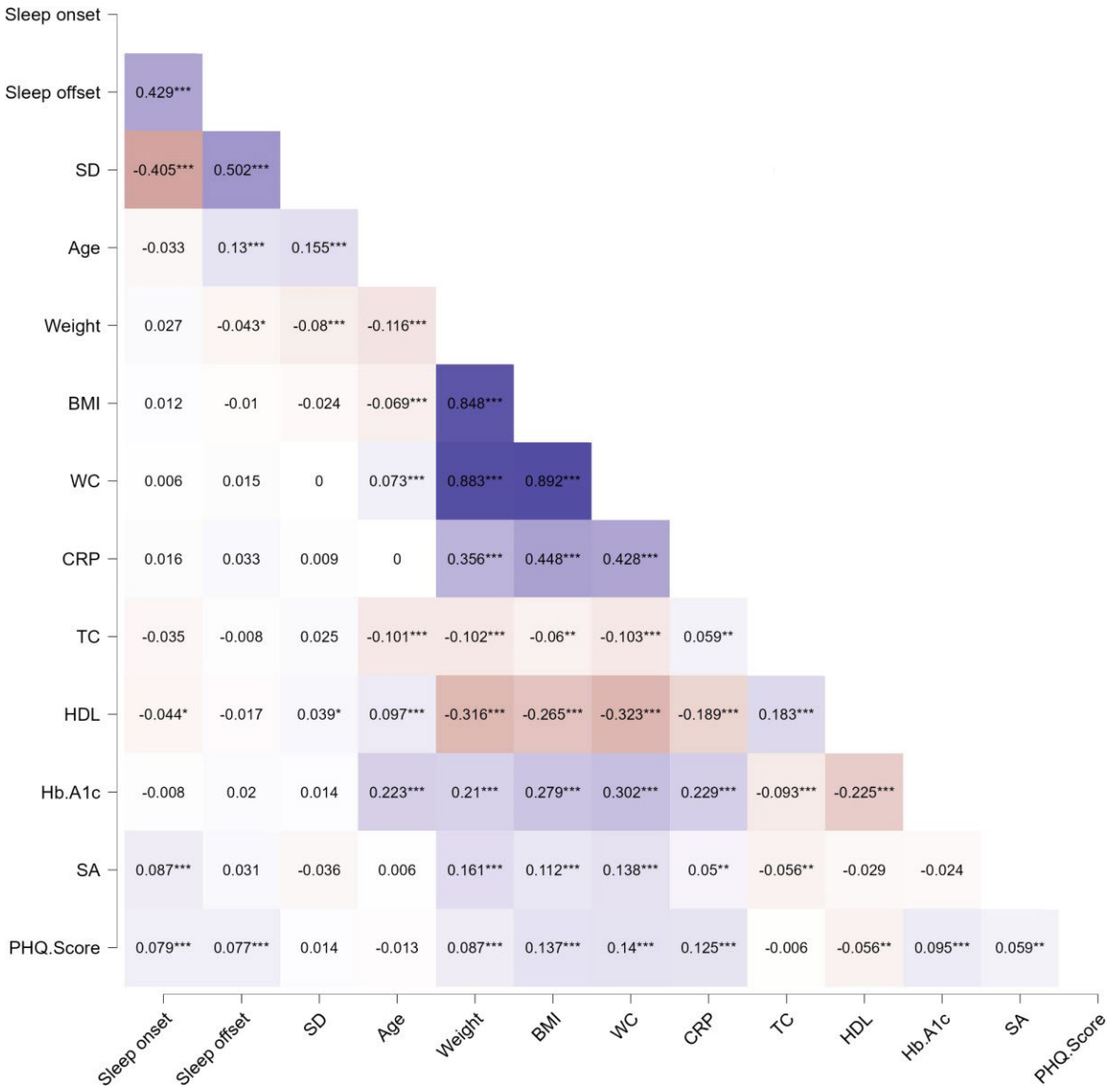
Note. (DS)- Daytime Sleepiness; (MRA)- Moderate Recreational Activity and (VRA)- Vigorous Recreational Activity.

Supplementary Table 2: List of 15 predictor variables selected in the final dataset

Attributes	Categories
Moderate Recreational Activity	Self-reported physical activity
Vigorous Recreational Activity	
Sedentary Activity	
Sleep onset	Self-reported sleep habits
Sleep offset	
Sleep duration	
Excessive daytime sleepiness	Indicative of sleep disturbance
Waist circumference	Anthropometric measurement
Body Mass Index	
C-reative protein	Plasma biomarkers of obesity
Total cholesterol	
High-density lipoprotein	
Glycated hemoglobin	Biomarker of diabetes
Sex	Sociodemographic characteristics
Age	

Supplementary Table 3: Glossary of key hyperparameters of machine learning models

XGBoost model specifications	**Maximum tree depth:** Specifies the maximum depth of the individual tree. **Boosting learning rate:** Specifies the boosting learning rate. The learning rate shrinks the contribution of each tree. **The number of trees:** Specifies how many gradient boosted trees will be included. A large number usually results in better performance. **Regularization strength:** Defines the cost strength of control over the model complexity to avoid overfitting. **Fraction of training instances:** Specifies the percentage of the training instances for fitting the individual tree. **Fraction of features for each tree:** Specifies the percentage of features to use when constructing each tree. **Fraction of features for each level:** Specifies the percentage of features to use for each level. **Fraction of features for each split:** Specifies the percentage of features to use for each split.
Random Forest model specifications	**Number of trees:** Specifies how many decision trees will be included in the forest. **Maximal number of considered features:** Number of attributes considered at each split. **Maximal tree depth:** The depth at which the trees will be grown. **Stop splitting nodes with maximum instances:** Specifies not to split subsets smaller than requested.
Logistic Regression Model Specifications	**Regularization type:** Regularization Lasso (L1). An alternative regularized version of the least squares method is Lasso (absolute minimum selection and shrinkage operator). **Regularization strength:** Sets the cost strength (default is C=1).



Supplementary Figure 1: Spearman's correlation between quantitative predictor variables and PHQ-9 score. (SD)- Sleep Duration; (BMI)- Body Mass Index; (WC)- Waist Circumference; (CRP)- C-Reactive Protein; (TC)- Total cholesterol; (HDL)- High Density Lipoprotein; (Hb. A1c)- Glycohemoglobin; (SA)- Sedentary Activity and (PHQ.Score)- PHQ-9 score. Note. * $p < .05$, ** $p < .01$, *** $p < .001$.