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Increased odds of metabolic syndrome among adults with depressive symptoms or antidepressant use

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Metabolic syndrome (MetS) is a condition that includes a cluster of risk factors for cardiovascular disease. In this paper, we aimed to evaluate the association between depressive symptoms, antidepressant use, duration of antidepressant use, antidepressant type and MetS. Data from the 2005–2018 National Health and Nutrition Examination Surveys were used in this study. Adults were included if they responded to the depressive symptoms and prescription medications questionnaires and had measures of blood pressure, waist circumference, triglycerides, high-density lipoprotein, and fasting plasma glucose. Participants were categorized by their antidepressant use (yes/no), type, and duration. This study included 14,875 participants (50.45% females), with 3616 (23.45%) meeting the criteria for MetS. Participants with higher depressive symptom scores (aOR = 1.04, 95% CI: 1.02, 1.05, $p < 0.001$) or those with depressive symptoms (aOR = 1.42, 95% CI: 1.17, 1.73, $p = 0.001$) had higher odds of MetS. A similar associations was seen among those who were on antidepressants compared to those who were not on antidepressants (aOR = 1.24, 95% CI: 1.03, 1.50, $p = 0.025$). Duration of antidepressant use was not significantly associated with MetS. Participants on tricyclic antidepressants had greater odds of MetS compared to those not taking any antidepressants (aOR = 2.27, 95% CI: 1.31, 3.93, $p = 0.004$). Our study provides evidence of the association between depressive symptoms, antidepressant use, and MetS, highlighting the importance of monitoring metabolic and cardiovascular alterations in individuals of depression.

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INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability with a worldwide prevalence of 280 million individuals [1]. Given the high burden of the disorder, treatment to mitigate the related symptoms is essential for enhanced functional recovery and optimal clinical outcomes [2]. Antidepressants are the first-line treatment option in MDD and are currently the most commonly prescribed medication in the United States (US) [3].

Aside from its symptoms, MDD's strong association with cardiovascular disease (CVD), diabetes, and metabolic syndrome (MetS) might make it one of the most challenging public health concerns [4]. MetS, in particular, is defined as a cluster of conditions including abdominal obesity, hypertension, dyslipidemia, and glucose intolerance [5]. The prevalence of MetS ranges from 20 to 43.5% in the general global population, and has an estimated prevalence of 33% in US adults [6]. MetS is also linked to an increased risk of CVD, type 2 diabetes mellitus (T2DM), subclinical atherosclerosis, target organ damage, and overall mortality, heightening the cause for concern when present in comorbidity with depression [7]. The pathophysiology of MetS is not fully known; however, insulin resistance, chronic inflammation, and neurohormonal activation are thought to be key factors in its development [8, 9]. While most studies have reported a positive

association between depression and MetS [10, 11], some studies have not found a significant link [12, 13].

Emerging evidence highlights significant links between depression, antidepressant use, and components of MetS, such as obesity, dyslipidemia, hypertension, and insulin resistance [14]. For instance, depression has been associated with increased levels of inflammatory markers, which can contribute to weight gain and altered lipid profiles [15, 16]. Antidepressant medications may also have a direct effect on MetS, as well as general negative consequences for cardiovascular risk [17]. Despite the fact that antidepressants are being prescribed at increasing rates, and there is evidence that these medications can induce weight gain [18], few studies have evaluated the association between antidepressant use and MetS. Crichton et al. (2016) indicated that the odds of MetS in patients who were on antidepressants were two-fold compared to patients who were not on antidepressants [19]. Moreover, Pyykkonen et al. (2012) investigated the correlations between depression symptoms, antidepressant use, and MetS. For each standard deviation increase in depressive symptoms score, the odds of having MetS increased by more than 10% [20]. The odds of having MetS also increased in participants who were on antidepressants by more than 50% [20]. In addition, longer antidepressant use has been associated with a higher incidence of antidepressant-related metabolic abnormalities [21, 22].

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Nevertheless, there is limited literature specifically on the association between duration of antidepressant use and MetS. Thus, there is a need to examine the association between MetS and antidepressant use irrespective of depression status.

Tricyclic antidepressants (TCAs) are one type of antidepressant that have been frequently reported to be associated with weight gain, increased appetite, and dyslipidemia – all of which can contribute to MetS [23]. In addition to TCAs, metabolic abnormalities and weight changes have been reported in selective serotonin reuptake inhibitor (SSRI) users [24, 25]. However, to the authors' knowledge, there has been no research on the association between MetS and antidepressant type or a comparison of the relationship with MetS across various antidepressant types.

Given the association between MDD and MetS, as well as the need to understand the relationship between antidepressant use and MetS, this study aims to investigate the associations between 1) depressive symptoms and MetS, 2) antidepressant use and MetS, 3) duration of antidepressant use and MetS, 4) antidepressant type and MetS. We hypothesize that depressive symptoms, antidepressant use, and long-term antidepressant use are associated with increased odds of MetS. Moreover, we hypothesize that participants on TCAs will have the greatest odds of MetS compared to participants who were not using any antidepressant.

METHOD

Study population and design

This study used cross-sectional population-based data from the 2005–2018 National Health and Nutrition Examination Surveys (NHANES). NHANES is a survey conducted by the US National Center for Health Statistics (NCHS) and the Center for Disease Control and Prevention. NHANES uses a complex, multistage probability sampling design to collect nationally representative data from the civilian non-institutionalized US population. Data were collected through in-home interviews using computer-assisted personal interviews and physical examinations performed at mobile examination centers (MEC). Participants provided signed consent prior to participation and the survey procedure was approved by the NCHS Research Ethics Review Board. Additional details about the survey protocol and sampling are presented on the CDC website: <https://www.cdc.gov/nchs/nhanes/>. We included participants who completed the Mental Health - Depression Screener questionnaire (DPQ) and Prescription Medications - Drug Information Questionnaire, were 18 years of age and older, reported fasting for 8.5–24 h, and had laboratory data for HDL, TG, and fasting plasma glucose. The sample size for this study was not determined through a formal power analysis. Instead, it was based on the availability of participants from the NHANES dataset. Given the comprehensive nature of the NHANES dataset, the sample size was considered adequate for the study objectives, consistent with prior research using similar data [26].

Exposure variables

Prescription drugs were categorized according to Cerner Multum's Lexicon, using a three-level hierarchical therapeutic classification system. Antidepressants were determined at the second level within the drug ingredient category, designated by code 249 [27]. A quantitative overview of antidepressant types, including a total of 39 specific generic names and drug IDs, is presented in Table S1. Participants who were using any of the antidepressants listed were classified as antidepressant users; otherwise, they were classified as non-users. Antidepressant users were further categorized by type and duration of antidepressant use. The antidepressant types in this study included SSRIs (serotonin, citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, duloxetine, levomilnacipran, venlafaxine, milnacipran), TCAs (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, clomipramine), atypical antidepressants (bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine, maprotiline, agomelatine), more than one type (participants taking more than one type from the following categories: SSRIs, SNRIs, TCAs, atypical antidepressants, pharmacological combinations, and monoamine oxidase inhibitors (MAOIs)), and non-users (reference group) [28]. Few participants were on MAOIs or pharmacological

combinations and were thus not included in the antidepressant type analysis, but were counted as "yes" for antidepressant use. Similarly, antidepressants that were reported as "unspecified" were categorized as "yes" for antidepressant use but could not be categorized into a specific type. Duration of antidepressant use was measured both as a continuous variable (number of days) and as a binary variable (>1 year or ≤1 year) [15–17].

Current depressive symptoms were evaluated using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a nine-item self-report questionnaire corresponding to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for MDD [24]. Participants answer each question on a scale of 0–3 based on their experience in the past two weeks. The overall severity of current depressive symptoms is measured by the sum of all item scores, providing a range from 0–27. A total score of 10 or more indicates the presence of clinically meaningful current depressive symptoms while a score of less than 10 indicates no depressive symptoms [29]. The validity and reliability of the PHQ-9 for MDD diagnosis have been confirmed through several studies [30, 31].

Outcome variable

The outcome of this study was MetS, dichotomized as MetS or no MetS, based on the National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) criteria. A participant was categorized as having MetS if they met three or more of the following criteria: waist circumference (BMXWAIST) > 88 cm in females or > 102 cm in males; triglycerides (TG) (LBXTR) > 150 mg/dL; blood pressure (BP) > 130/85 mmHg; high-density lipoprotein (HDL) (LBDHDD) < 40 mg/dL in females or < 50 mg/dL in males; fasting plasma glucose (LBXGLU) > 100 mg/dL [6]. Systolic and diastolic BP were calculated as the mean of available values from three systolic BP measures (BPXSY1, BPXSY2, BPXSY3) and three diastolic BP measures (BPXDI1, BPXDI2, BPXDI3). Outcome measures that required participants to fast included plasma glucose and TG.

Due to laboratory and/or device changes to measure fasting plasma glucose from 2005–2018, adjustment equations were applied, as recommended by NHANES. The 2005–2006 fasting plasma glucose values (Roche 911 device) were adjusted using Eq. 1 [32] and the 2015–2016 and 2017–2018 values (Cobas C311 device) were adjusted using Eq. 2 [33]. The 2007–2012 (Roche ModP device) and 2013–2014 (Cobas C501 device) values did not have recommendations for adjustment, nor did the other lab values used to define MetS.

$$Y(\text{Roche ModP}) = X(\text{Roche 911}) + 1.148 \quad (1)$$

$$Y(\text{Cobas C501}) = 0.9776 * X(\text{Cobas C311}) + 0.4994 \quad (2)$$

Covariates

Covariates were included to adjust for their potential influence on the outcome of interest. Covariates included age (treated as continuous) [34], sex (male or female) [34], ratio of family income to poverty (PIR; low income < 1, middle income 1 to 4, or high income > 4) [35], race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race including multi-racial) [34], education (less than 9th grade, 9th–11th grade, high school graduate/General Educational Development (GED), some college/Associate of Arts (AA) degree, or college graduate or above) [36], marital status (never married, married, widowed, divorced, separated, or living with a partner) [37], smoking status (non-smoker or smoker) [38], drinking status (never drinker, light drinker, moderate drinker, or heavy drinker) [38], and history of health indicators such as congestive heart disease, coronary heart disease, angina, heart attack, hypertension, diabetes, and stroke [39]. The presence of these diseases was treated as a binary variable, with 'Yes' indicating the presence and 'No' indicating the absence of the condition. Depressive symptoms, depressive symptom severity, and antidepressant use were included when applicable.

Statistical analysis

Statistical analyses were performed using R v 4.4.0, along with the 'survey' package (version 4.4–2) [40]. To account for the NHANES complex survey design, fasting subsample survey weights (WTSF2YR) were used due to the use of the fasting plasma glucose and triglycerides variables in defining MetS. The analysis applied the primary sampling unit variable (SDMVPSU)

Table 1. Demographic characteristics, stratified by presence of metabolic syndrome ($n = 14,875$).

Characteristic	Total	No MetS	MetS	p-value
Sample Size	14,875	11,259	3616	–
Total PHQ-9 score (mean (SD))	2.93 (3.92)	2.73 (3.71)	3.58 (4.48)	<0.001
Depressive symptom (%)				<0.001
No	13,652 (92.91)	10,483 (93.91)	3169 (89.64)	
Yes	1223 (7.09)	776 (6.09)	447 (10.36)	
Antidepressant use among people with depressive symptoms (%)				0.148
No	816 (60.56)	541 (62.39)	275 (57.04)	
Yes	407 (39.44)	235 (37.61)	172 (42.96)	
Antidepressant use (%)				<0.001
No	13,297 (86.68)	10,235 (88.25)	3062 (81.56)	
Yes	1578 (13.32)	1024 (11.75)	554 (18.44)	
Antidepressant type (%)				<0.001
Non-user	13,297 (86.74)	10,235 (88.28)	3062 (81.70)	
SSRIs	817 (6.93)	545 (6.32)	272 (8.92)	
SNRIs	206 (1.86)	139 (1.64)	67 (2.58)	
TCAs	108 (0.73)	54 (0.48)	54 (1.55)	
Atypical antidepressants	223 (1.82)	148 (1.69)	75 (2.25)	
More than one type	216 (1.92)	134 (1.59)	82 (3.00)	
Duration of antidepressant - in days (mean(SD))	1915.53 (2212.73)	1845.44 (2188.78)	2061.09 (2256.83)	0.189
Duration of antidepressant (%)				0.600
≤one year	520 (31.29)	348 (31.92)	172 (29.99)	
>one year	1040 (68.71)	665 (68.08)	375 (70.01)	
Age (mean (SD))	46.23 (17.35)	44.82 (17.63)	50.84 (15.54)	<0.001
Sex (%)				0.721
Male	7377 (49.55)	5643 (49.44)	1734 (49.93)	
Female	7498 (50.45)	5616 (50.56)	1882 (50.07)	
PIR (%)				<0.001
Middle income	7321 (50.13)	5448 (48.99)	1873 (53.84)	
Low income	2880 (13.99)	2115 (13.69)	765 (14.96)	
High income	3479 (35.88)	2790 (37.31)	689 (31.20)	
Race (%)				<0.001
Mexican American	2476 (8.64)	1750 (8.12)	726 (10.34)	
Other Hispanic	1478 (5.47)	1075 (5.50)	403 (5.38)	
Non-Hispanic White	6381 (67.87)	4702 (67.05)	1679 (70.54)	
Non-Hispanic Black	2979 (10.86)	2451 (11.72)	528 (8.08)	
Other Race - Including Multi-Racial	1561 (7.15)	1281 (7.61)	280 (5.67)	
Education (%)				<0.001
Less than 9th grade	1377 (4.93)	920 (4.44)	457 (6.50)	
9–11th grade	2292 (11.53)	1673 (11.03)	619 (13.14)	
High school graduate/ GED	3538 (24.23)	2630 (23.26)	908 (27.34)	
Some college/ AA degree	4127 (30.45)	3062 (29.74)	1065 (32.71)	
College graduate or above	3318 (28.87)	2763 (31.52)	555 (20.32)	
Marital status (%)				<0.001
Married	7404 (55.49)	5429 (54.41)	1975 (58.93)	
Widowed	1030 (5.25)	697 (4.61)	333 (7.30)	
Divorced	1499 (10.15)	1053 (9.61)	446 (11.88)	
Separated	468 (2.26)	352 (2.30)	116 (2.15)	
Never married	2638 (18.20)	2221 (20.23)	417 (11.76)	
Living with partner	1210 (8.64)	928 (8.84)	282 (7.99)	
Smoking status (%)				0.008
Non-smoker	11,488 (80.19)	8696 (80.81)	2792 (78.18)	

Table 1. continued

Characteristic	Total	No MetS	MetS	p-value
Smoker	2831 (19.81)	2050 (19.19)	781 (21.82)	
Drinking status (%)				<0.001
Never drinker	4614 (25.66)	3255 (23.58)	1359 (32.33)	
Light drinker	2950 (19.18)	2145 (18.18)	805 (22.41)	
Moderate drinker	4890 (38.29)	3821 (39.69)	1069 (33.81)	
Heavy drinker	1966 (16.87)	1623 (18.55)	343 (11.45)	
Congestive heart failure (%)				<0.001
No	13,583 (97.66)	10,233 (98.35)	3350 (95.48)	
Yes	429 (2.34)	239 (1.65)	190 (4.52)	
Coronary heart disease (%)				<0.001
No	13,422 (96.51)	10,108 (97.20)	3314 (94.32)	
Yes	563 (3.49)	345 (2.80)	218 (5.68)	
Angina (%)				<0.001
No	13,639 (97.74)	10,253 (98.35)	3386 (95.84)	
Yes	356 (2.26)	202 (1.65)	154 (4.16)	
Heart attack (%)				<0.001
No	13,417 (96.54)	10,111 (97.23)	3306 (94.37)	
Yes	603 (3.46)	362 (2.77)	241 (5.63)	
Hypertension (%)				<0.001
No	10,693 (74.74)	8655 (79.55)	2038 (59.03)	
Yes	4141 (25.26)	2577 (20.45)	1564 (40.97)	
Diabetes (%)				<0.001
No	13,061 (91.05)	10,317 (94.50)	2744 (79.83)	
Yes	1802 (8.95)	933 (5.50)	869 (20.17)	
Stroke (%)				<0.001
No	13,531 (97.22)	10,158 (97.65)	3373 (95.87)	
Yes	495 (2.78)	317 (2.35)	178 (4.13)	

Continuous characteristics reported as weighted mean and standard deviation.

Categorical characteristics reported as unweighted frequency and weighted percent.

The first level of categorical variables is the reference level.

SSRIs include: serotonin, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. SNRIs include: desvenlafaxine, duloxetine, levomilnacipran, venlafaxine, and milnacipran. TCAs include: amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, and clomipramine. Atypical antidepressants include: bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine, maprotiline, and agomelatine. 'More than one type' includes participants who take more than one type from the following categories: SSRIs, SNRIs, TCAs, atypical antidepressants, antidepressants-unspecified, MAOs, and pharmacological combinations. MAOs include isocarboxazid, phenelzine, selegiline, tranylcypromine, and monoamine oxidase inhibitors - unspecified. Pharmacological combinations include amitriptyline with chlordiazepoxide, amitriptyline with perphenazine, fluoxetine with olanzapine, and bupropion with naltrexone.

PHQ-9 nine-item patient health questionnaire, *PIR* ratio of family income to poverty, *SD* standard deviation.

P-values < 0.05 denote significant differences between no MetS vs. MetS, and are reported as weighted *p*-values.

and the strata variable (SDMVSTRA), with the fasting survey weights adjusted by dividing by seven (WTSF2YR/7) to account for the aggregation of seven survey cycles, as suggested by NHANES (<https://www.cdc.gov/nchs/nhanes/tutorials/weighting.aspx>). In the table and figure summarizing demographic characteristics, variables were presented using unweighted frequencies (generated using the CreateTableOne() function from the 'tableone' package, version 0.13.2 [41] and weighted percentages (obtained via the svyCreateTableOne() function).

T-tests were used to compare continuous variables among those with versus without MetS, and χ^2 tests were used to compare categorical variables. Statistical significance was set to $P < 0.05$ using two-tailed hypothesis testing. Unadjusted and adjusted logistic regression models were used to estimate the association between current depressive symptom severity (total PHQ-9 scores), current depressive symptoms (yes/no), antidepressant use, antidepressant type, and duration of antidepressant use with MetS. A logarithmic transformation was applied to the duration of antidepressant use (in days) to meet model assumptions. Covariates for the multivariable logistic regression models were selected based on clinical relevance, guided by our prior knowledge, team expertise, and findings from the literature.

RESULTS

Study sample

In this study, we included 14,875 participants aged 18–85 years, of which 7498 (50.45%) were females and 3616 (23.45%) met the criteria for MetS (Table 1). The weighted mean age of participants with and without MetS was 50.84 (SD = 15.54) and 44.82 (SD = 17.63) years, respectively. Out of 14,875 participants, 1223 (7.09%) were categorized as having depressive symptoms. Moreover, among the 407 (39.44%) individuals with depressive symptoms who were on antidepressants, 172 (42.96%) met the criteria for MetS. There were significant differences between the MetS and no MetS groups for all covariates except depressive symptoms treated with antidepressants, duration of antidepressant use (continuous and binary), and sex. Figure 1 is a flow chart of participants' inclusion in the study. Table 1 shows the demographic characteristics of the study population. Figure 2 shows the characteristics of variables used to define MetS with weighted

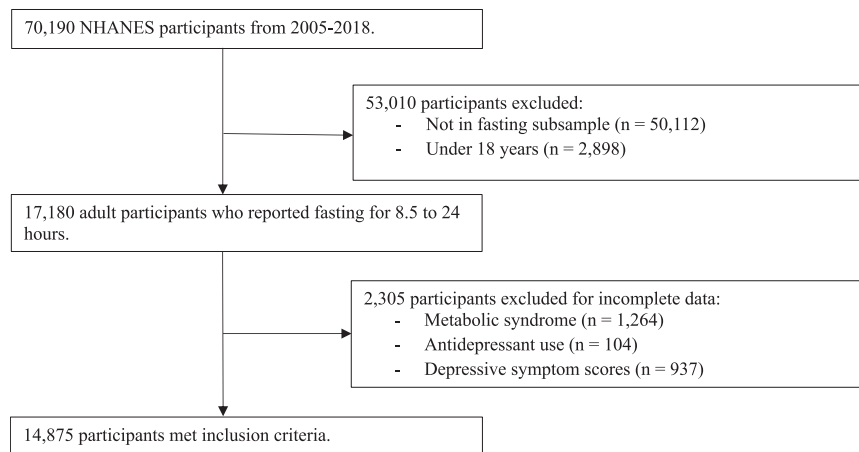


Fig. 1 Flow chart of participant inclusion into the study.

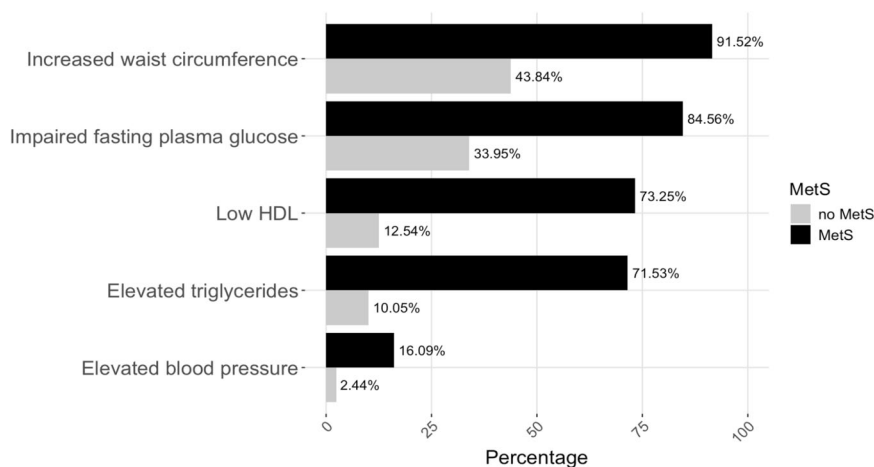


Fig. 2 Distribution of metabolic syndrome components by presence of metabolic syndrome. Values are reported as weighted percentages. Each variable is compared against clinically defined reference levels. Specifically: Increased waist circumference: >88 cm in females, >102 cm in males; Impaired fasting plasma glucose: Fasting plasma glucose > 100 mg/dL; Low HDL: <40 mg/dL in females, <50 mg/dL in males; Elevated triglycerides: >150 mg/dL; Elevated blood pressure: >130/85 mm Hg.

Table 2. Main effects models for association between the presence of MetS and current depressive symptom severity (total PHQ-9 scores), current depressive symptoms (yes/no), and antidepressant use.

MetS (yes/no)				
Exposure group	OR (95% CI)	p-value	aOR (95% CI)	p-value
Total PHQ-9 scores ^{1a}	1.05 (1.04, 1.06)	<0.001	1.04 (1.02, 1.05)	<0.001
Antidepressant use - yes ^{1b}	1.70 (1.46, 1.97)	<0.001	1.24 (1.03, 1.50)	0.025
Depressive symptoms - yes ^{2a}	1.78 (1.51, 2.10)	<0.001	1.42 (1.17, 1.73)	0.001
Antidepressant use - yes ^{2b}	1.70 (1.46, 1.97)	<0.001	1.31 (1.09, 1.57)	0.004

OR unadjusted odds ratio, aOR adjusted odds ratio, CI confidence interval, the reference level for depressive symptoms is "no". ^{1a}Covariates in adjusted models include all 15 pre-selected covariates and antidepressant use. ^{1b}Covariates in adjusted models include all 15 pre-selected covariates and depressive symptom severity (total PHQ-9 scores). ^{2a}Covariates in adjusted models include all 15 pre-selected covariates and antidepressant use. ^{2b}Covariates in adjusted models include all 15 pre-selected covariates and depressive symptoms (yes/no). *p*-values < 0.05 denote statistical significance.

percentages. Table S1 lists all types of antidepressants from the second level of drug ingredient category code 249, including predefined antidepressant types, specific medication names, drug IDs, and the number of participants taking each type of antidepressant in the study. Table S2 presents the raw frequencies and weighted percentages of different antidepressant types, stratified by antidepressant use within the depressive symptom groups.

Current depressive symptoms and MetS

Participants with higher total PHQ-9 scores had greater odds of having MetS (adjusted odds ratio (aOR) = 1.04, 95% CI: 1.02, 1.05, *p* < 0.001; Table 2). Similarly, participants with current depressive symptoms had 42% higher odds of having MetS (aOR = 1.42, 95% CI: 1.17, 1.73, *p* = 0.001) compared to those without current depressive symptoms when adjusting for all 15 pre-selected covariates and antidepressant use (Table 2). However, among participants with

Table 3. Main effects models for association between the presence of MetS and antidepressant type.

MetS (yes/no)				
Antidepressant type	OR (95% CI)	p-value	aOR (95% CI)	p-value
SSRIs	1.53 (1.24, 1.88)	<0.001	1.18 (0.92, 1.53)	0.190
SNRIs	1.70 (1.12, 2.57)	0.013	1.24 (0.80, 1.93)	0.331
TCA	3.49 (2.29, 5.32)	<0.001	2.27 (1.31, 3.93)	0.004
Atypical antidepressants	1.44 (1.02, 2.04)	0.040	1.08 (0.73, 1.61)	0.694
More than one type	2.03 (1.46, 2.83)	<0.001	1.19 (0.84, 1.69)	0.317

OR unadjusted odds ratio, aOR adjusted odds ratio, CI confidence interval, the reference level for antidepressant type is “non-user”. Covariates in adjusted models include all 15 pre-selected covariates and depressive symptom severity (total PHQ-9 scores). *p*-values < 0.05 denote statistical significance.

depressive symptoms, antidepressant use was not significantly associated with the presence of MetS compared to those not on antidepressants (aOR = 0.80, 95% CI: 0.55, 1.17, *p* = 0.255; Table S3).

Antidepressant use/duration and MetS

In the unadjusted model, participants who were on antidepressants had higher odds of having MetS compared to those who were not on antidepressants. This association persisted after adjusting for all 15 covariates, as well as either total PHQ-9 scores (aOR = 1.24, 95% CI: 1.03, 1.50, *p* = 0.025) or current depressive symptoms (aOR = 1.31, 95% CI: 1.09, 1.57, *p* = 0.004; Table 2). Among participants on antidepressants, the odds of having MetS did not significantly differ based on whether antidepressants were taken for more than one year compared to one year or less (aOR = 1.15, 95% CI: 0.65, 2.04, *p* = 0.622; Table S4). Similarly, no significant association was found between the duration of antidepressant use (log-transformed days) and the odds of having MetS (aOR = 1.07, 95% CI: 0.67, 1.70, *p* = 0.775; Table S4).

Antidepressant type and MetS

Participants using TCAs had higher odds of having MetS compared to those not taking any antidepressants after adjusting for all 15 covariates as well as total PHQ-9 scores (aOR = 2.27, 95% CI: 1.31, 3.93, *p* = 0.004; Table 3). No significant associations were found between MetS and the use of SNRIs, SNRIs, Atypical antidepressants, or more than one type of antidepressant compared to non-users in the adjusted models (Table 3).

DISCUSSION

In this study, we used the NHANES dataset to evaluate the associations of MetS with depressive symptoms, antidepressant use, duration of antidepressant use, and antidepressant type. The results of our study indicated that participants had greater odds of MetS when they experienced depressive symptoms compared to those without depressive symptoms. Participants who were on antidepressants also had greater odds of having MetS compared to those who were not on antidepressants. Across the different types of antidepressants, only participants on TCAs had significantly greater MetS odds compared to those who were not using any antidepressant.

The results of our study are consistent with previous studies reporting that depression is positively associated with MetS [11, 12, 17, 42–44]. Patients with psychiatric disorders, including depression and anxiety, are at a higher risk of CVD and physical disorders with an increased likelihood of risk factors including unhealthy lifestyle factors (smoking, poor diet, alcohol use), behavioral inactivation, and social isolation [45–48]. Several pathophysiological mechanisms could explain the association between depression and MetS. Depression and MetS have both been linked to excessive hypothalamic-pituitary-adrenal axis activation, which results in excessive

cortisol release [49]. An indirect pathway from depression to MetS involves unhealthy behaviors associated with depression, including cigarette smoking, alcohol use, and physical inactivity, which increase the risk of MetS and CVD [45, 50]. MetS has also been associated with greater depressive symptom severity [51]. This relationship may also be bidirectional, such that the presence of MetS might precede that of depression. However, the cross-sectional nature of this study precludes an examination of the directionality of this association. This study reported that the prevalence of MetS in individuals with depressive symptoms is 34.27% which contrasts the results from Rethorst et al. who reported a 41.1% incidence of MetS using 2009–2010 NHANES data [52]. This difference may arise from variations in sample characteristics; Rethorst et al. included individuals with PHQ-9 scores ≥ 10 and examined elevated inflammation (C-reactive protein (CRP) levels) alongside MetS [52]. Their results showed higher MetS prevalence in participants with elevated CRP, potentially indicating an association between inflammation and MetS in individuals with more severe depression. This nuance may account for the variation in MetS prevalence. However, findings from a meta-analysis by Vancampfort et al. on 5531 individuals with depression align with our findings, with 30.5% of participants meeting the criteria for MetS [53].

We hypothesized that participants with depressive symptoms who were on antidepressants would have higher odds of MetS compared with those with depressive symptoms who were not on antidepressants. While our study did not find a statistically significant association (aOR = 0.80, 95% CI: 0.55, 1.17), the effect size suggests a potential association between antidepressant use and a reduced likelihood of MetS, though the confidence interval includes the possibility of a 17% increase in the likelihood of MetS. These results differ from a study by Corruble et al. which compared the incidence of MetS in patients with MDD before and after the initiation of antidepressants [54]. The lack of significance in our study may reflect the predominance of non-TCA agents, which are often associated with fewer metabolic side effects than TCAs. Our findings indicated that out of the 407 participants with depressive symptoms who were using antidepressants, 194 participants were using SSRIs, 53 participants were using SNRIs, 14 participants were using TCAs, 57 participants were using atypical antidepressants, and 89 participants were using more than one type of antidepressants. Moreover, other factors that were not measured by NHANES, such as the lifetime duration of prior antidepressant medication use, could have influenced our results.

Antidepressants, as the most common treatment for depression, can cause weight gain, metabolic abnormalities such as dyslipidemia, increased appetite, insulin resistance, and decreased basal metabolic rate, which may, in turn, contribute to MetS [22, 23, 47]. Our adjusted results indicate that antidepressant use was associated with a 24–31% increase in odds of MetS among participants with depressive symptoms, which underscores the

clinical relevance of this association. The increase in MetS risk may reflect both the direct metabolic side effects of antidepressants and the potential for antidepressant-related weight gain, particularly for patients experiencing increased appetite during treatment [19, 55]. Significant weight gain during the initial stage of antidepressant therapy, or weight gain that persists beyond the remission of depression symptoms, is likely a side effect of treatment [42]. Antidepressant use is also associated with increased systolic BP, TG, and waist circumference, which are all involved in MetS [42]. As aforementioned, antidepressants are among the most commonly prescribed medications [3]. Therefore, administering treatments with the lowest association with MetS is essential, especially in patients who are at higher risk for MetS, such as the elderly and those with chronic diseases such as T2DM and HTN.

Our study found that participants on TCAs have significantly higher odds of MetS compared to participants with no antidepressant use. TCA use has multiple side effects, such as HTN through peripheral $\alpha 1$ adrenergic receptor agonism [56]. TCAs also have antihistaminergic effects that may result in weight gain and subsequent dyslipidemia [42]. Finally, TCAs decrease the basal metabolic rate and cause increased appetite and carbohydrate craving, which are associated with T2DM and possible insulin resistance [57]. However, it is important to interpret this result cautiously. The number of participants taking TCAs was relatively small, which may limit the generalizability of these findings. Moreover, TCAs are typically prescribed for patients with more severe depression, which itself is associated with increased metabolic risk [58]. However, it should be noted that TCAs are typically non-first-line treatments for depression and have indications beyond depression, including chronic pain syndromes, such as migraine and fibromyalgia, as well as obsessive-compulsive disorder (OCD), which also have positive associations with MetS and CVD [59, 60]. These potential comorbidities may confound the relationship between TCA use and MetS, as patients with these conditions could be predisposed to higher metabolic risk regardless of TCA use. Future research with a larger sample of TCA users and detailed data on comorbid conditions could help clarify the specific contribution of TCAs to MetS risk.

This specific study aimed to compare the odds of MetS in each antidepressant class relative to individuals not using antidepressants. The insignificant results pertaining to SSRI, SNRI, and atypical antidepressant use may be due to inconsistent metabolic effects within these antidepressant classes compared to the no-antidepressant group. For example, SSRIs can cause weight gain and increased waist circumference, increased serum TG levels, higher low-density lipoprotein cholesterol (LDL-C), abnormal glucose tolerance, and insulin resistance [42, 61]. Randomized clinical trials have reported minimal effects of bupropion, mirtazapine, nefazodone, and trazodone on BP [62, 63]. Bupropion, nefazodone, and trazodone are often considered 'weight neutral' and a growing body of evidence suggests that bupropion may promote weight loss [64, 65]. Moreover, these medications do not have clinically significant impacts on lipid and glucose metabolism [66].

Current guidelines for the treatment of depression, including the Canadian Network for Mood and Anxiety Treatments (CANMAT), American Psychiatric Association (APA), and National Institute for Health and Care Excellence (NICE) guidelines, do not include MetS in side effect monitoring or patient counseling [67–69]. Taking into account the scope of literature suggesting an association between antidepressant use and MetS, including this study, as well as the implications of MetS in increasing the risk of adverse cardiovascular, endocrine, and ischemic outcomes [70, 71], it may be important to consider the risk of MetS in future iterations of these guidelines to include recommendations on counseling and interval monitoring of waist circumference, lipid profile, glucose, and BP.

Despite the fact that the NHANES dataset offers a large sample size and the use of survey weights to enhance representativeness of the US population, our findings may be affected by the limitations of the data collection methods. Only a portion of the sample provided fasting blood samples, which allowed for MetS identification. A study using data from the 2009–2010 NHANES cycle reported that the fasting participant subsample had a lower body mass index and waist circumference than the non-fasting sample [52]. If this is also the case for the participants from the additional survey cycles included in the current study, this could mean that the rate of MetS demonstrated in our sample may be an underestimate of the true prevalence of MetS. While survey weights help to account for sampling biases, potential differences between fasting and non-fasting groups may still limit generalizability. Moreover, the cross-sectional design of the data limits our results to associations rather than causative conclusions. Cross-sectional studies using self-report questionnaires are also subject to non-response bias. For instance, it is possible that some individuals with clinically diagnosed depression did not complete the DPQ if the questionnaire raised feelings of discomfort. These participants would have been excluded from the current study, which can potentially skew results. Antidepressant use was self-reported and, although the majority of these drugs were validated using medication containers, some misclassification may have occurred [68]. Nonetheless, identifying these associations is a critical first step in understanding the complex interplay between depressive symptoms, antidepressant use, and MetS. This foundation will guide future research aimed at uncovering causal mechanisms, which could ultimately inform clinical guidelines and interventions. Additionally, while the NHANES dataset provides a robust range of variables, some potentially relevant covariates identified through the literature review were unavailable. These include medical conditions such as chronic pain [60], autoimmune disorders (e.g., lupus) [72], chronic inflammatory conditions (e.g., inflammatory bowel disease) [73], and neurological conditions (e.g., migraines or epilepsy) [74], which have been reported to influence both metabolic syndrome and depression in prior studies. Additionally, psychosocial stress [75], and trauma history [76] were identified as relevant but were not captured in the NHANES data used for this study. The absence of these variables represents a limitation, which we acknowledge in the interpretation of our findings. Further limitations include our inability to assess the effects of specific antidepressants, dosage, or treatment duration, as well as the possibility that some participants used antidepressants for non-depressive conditions. Despite these limitations, the objective measurement of anthropometric data and MetS parameters, as well as the use of survey weights, strengthens our study. Future research should investigate the potential impact of individual medications, dosages, and the reasons for antidepressant use on metabolic syndrome outcomes to provide more nuanced insights.

In conclusion, this study demonstrated positive associations between depressive symptoms and MetS, as well as between overall antidepressant use—particularly TCA use—and MetS, using 2005–2018 NHANES data. More research into the underlying mechanisms of this phenomenon is needed. Future studies should further evaluate the odds of MetS in individuals with depressive symptoms treated with antidepressants and with long-term antidepressant use. Moreover, further research comparing different antidepressant types is needed to determine the most appropriate treatments for patients at high risk of CVD and MetS.

DATA AVAILABILITY

We used data from NHANES which is publicly available via <https://www.cdc.gov/nchs/nhanes/index.htm>. The statistical analysis plan and analytic code that supports the findings of this study are available from the corresponding author, VB, upon reasonable request.

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AUTHOR CONTRIBUTIONS

SM conceptualized the study and was responsible for project administration, methodology, investigation, writing the original draft, and reviewing and editing the manuscript. SFD contributed to conceptualization, methodology, formal analysis, writing the original draft, and reviewing and editing the manuscript. VKT contributed to conceptualization and manuscript review and editing. QL was responsible for formal analysis and manuscript review and editing. HYMP, HJ, and WL contributed to manuscript review and editing, with WL also supervising the study. VB conceptualized the study and was responsible for project administration, methodology, investigation, supervision, writing the original draft, and reviewing and editing the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

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ETHICS

The survey protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics (protocol numbers 2005–06, 2011–17, 2018–01). Written informed consent was obtained from participants prior to data collection. All methods were performed in accordance with the relevant guidelines and regulations.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41398-025-03289-4>.

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