

ORIGINAL RESEARCH

Sex-based epidemiological differences in depression and metabolic dysfunction in U.S. adults—NHANES 2017–2020

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Abstract

Background: The presence of metabolic dysfunctions defines metabolic syndrome. While the epidemiology of depression and metabolic abnormalities has been studied, the role of sex remains unclear. **Methods:** Adults aged 20 and above (N = 3162 (202,474,260 after weighting)) from the 2017–2020 National Health and Nutrition Examination Survey were included. Depression severity was measured using the Patient Health Questionnaire-9 (PHQ-9) score, which was first treated as a continuous variable, with restricted cubic splines plotted. It was then analyzed as quartiles and four levels, adjusting for covariates. The first percentile and non-depressed individuals served as the reference group. **Results:** Subgroup analyses revealed distinct sex-specific associations between depression severity and metabolic dysfunction. In females, clinical threshold analysis showed increased diabetes (moderate: OR = 2.45, 95% CI: 1.22–4.93, Q: 0.048) and hypertension (moderate: OR = 2.75, 95% CI: 1.27–5.94, Q: 0.042). In males, major depression was strongly associated with metabolic syndrome (OR = 4.83, 95% CI: 2.26–10.31, Q: 0.003), hypertension (OR = 4.23, 95% CI: 1.80–9.98, Q: 0.009), and hypertriglyceridemia (OR = 3.53, 95% CI: 1.37–9.10, Q: 0.039). Quartile analysis showed that in males, the highest depression quartile (Q4) was also linked to non-alcoholic fatty liver disease (NAFLD (OR = 2.42, 95% CI: 1.46–4.01, Q: 0.006)) and metabolic dysfunction-associated steatotic Liver Disease (MASLD (OR = 2.22, 95% CI: 1.44–3.42, Q: 0.003)). **Conclusions:** Depression is associated with sex-specific metabolic risks: in females, risk is most pronounced at the moderate severity threshold, centered on diabetes and hypertension; in males, risk shows a severity-dependent gradient, strongest for metabolic syndrome, hypertension, hypertriglyceridemia, and fatty liver diseases.

Keywords

Depression; Metabolic syndrome; Sex differences

1. Introduction

Depression is a common mental disorder and a leading cause of psychological and physical disability worldwide, with its prevalence exhibiting a concerning upward trajectory globally [1, 2]. It significantly impairs quality of life and is a well-established risk factor for suicide. Notably, depression substantially reduces life expectancy across all age groups. For instance, in the United States, approximately 1.4 million suicide attempts occur annually, with about 60% of all suicides being attributable to mood disorders [3, 4].

Metabolic syndrome (MS) is characterized by obesity, dyslipidemia, high blood pressure, and elevated fasting blood glucose [5]. Although the prevalence of metabolic syndrome varies across different regions of the world, ranging from 32.4% in Africa to 41.9% in Canada, its impact on health and its high prevalence have made it a major public health issue.

Although the prevalence of metabolic syndrome varies across different regions of the world, ranging from 32.4% in Africa to 41.9% in Canada, its impact on health and its high prevalence have made it a major public health issue [6]. A complex and bidirectional relationship between depression and MS has been increasingly recognized, suggesting shared pathophysiological pathways such as obesity, hypothalamic-pituitary-adrenal axis dysregulation, and lifestyle factors [7–9].

While the epidemiology of depression and metabolic syndrome has been studied, a pivotal yet often underexplored dimension in this interplay is sex. Substantial evidence indicates notable sex disparities in both the prevalence and manifestation of depression and metabolic disorders [10, 11]. Nevertheless, previous epidemiological studies have frequently overlooked or insufficiently analyzed the moderating role of sex in the depression-MS relationship, resulting in a knowledge gap.

Therefore, to address this topic, this study aimed to inves-

tigate the sex-specific associations between depression and metabolic syndrome and its individual components among U.S. adults using recent national representative data.

2. Methods

2.1 Study population

The study population in this article is derived from the National Health and Nutrition Examination Survey (NHANES) in the United States. NHANES is a periodic cross-sectional survey conducted by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC), aimed at assessing the health and nutrition status of the U.S. population. The data comes from health interviews and health measurements, with health interviews conducted at participants' homes and health measurements taken at equipped mobile centers. The sample design consists of a multiyear, stratified, clustered four-stage sample representing the non-institutionalized civilian population living in the 50 states and the District of Columbia [12]. The NCHS Ethics Review Board has approved all NHANES surveys. Our study is based on data collected during the NHANES 2017–2020 cycle and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational epidemiological studies.

2.2 Sex

Sex typically refers to biological characteristics related to physical and physiological aspects, including chromosomal composition, hormone levels, and internal and external anatomical features. In this article, sex is defined within a binary framework, which is generally determined by genetics and assigned at birth based on observable biological differences. Therefore, the findings in this article are specifically applicable to individuals within the binary sex classification. Considering the similarity in their definitions, we included both in the analysis for sensitivity analysis.

2.3 PHQ-9 score

PHQ-9 scores from the NHANES database were used to quantify depression levels. The PHQ-9 score is a commonly used self-reported scale, with scores ranging from 0 to 27, to assess the frequency of depressive symptoms over the past two weeks. It is designed based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and is considered one of the most reliable tools for screening depression. Research has demonstrated that it has good reliability and validity in the screening of depression [13–15]. Data was entered by trained interviewers at the Mobile Examination Center (MEC) using the Computer Assisted Personal Interview (CAPI) system, which includes built-in consistency checks to reduce data entry errors.

2.4 Metabolic syndrome and related metabolic dysfunction

According to the 2005 National Triglyceride Education Program Adult Treatment Panel III (ATP III) guidelines, MS can

be diagnosed if three or more of the following five criteria are met [16]:

- Increased abdominal circumference, ≥ 102 cm (≥ 40 in) (male) and ≥ 90 cm (≥ 35 in) (female);
- Low plasma level of high-density lipoprotein (HDL)-cholesterol, < 1.04 mmol/L (< 40 mg/dL) (male) and < 1.30 mmol/L (< 50 mg/dL) (female);
- Increased values for plasma triglycerides, ≥ 1.70 mmol/L (≥ 150 mg/dL);
- Elevated blood pressure, $\geq 130/85$ mmHg;
- Fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

We will analyze MS and each of its five components separately. Abdominal obesity (AOB) is defined as a waist circumference ≥ 102 cm (male) or ≥ 90 cm (female), Low HDL-cholesterol (LHDL-C) is defined as < 1.04 mmol/L (male) or < 1.30 mmol/L (female), and elevated triglyceride (Hypertriglyceridemia (HTG)) is defined as plasma triglyceride ≥ 1.7 mmol/L. Current guidelines typically define hypertension as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Obesity (OB), as determined by (body mass index) BMI ≥ 30 , a commonly used measure of obesity, was also included in the analysis. Therefore, for the analysis of hypertension (HBP), we use 140/90 mmHg as the cutoff value and include patients who have previously been diagnosed with hypertension or are currently taking antihypertensive medication [17]. The diagnosis of diabetes mellitus (DM) follows the criteria provided by the American Diabetes Association, which is fasting blood glucose ≥ 7.0 mmol/L or glycated hemoglobin (HbA1c) $\geq 6.5\%$, including patients who have been diagnosed with diabetes or are currently on medication [18].

Blood lipid levels are continuous variables that vary with factors such as sex, age, environment, and diet and are usually the result of the interaction of various pathological and non-pathological factors. Due to the lack of an accurate definition of hyperlipidemia, following the recommendation of Fernando Civeira *et al.* [19], hyperlipidemia (HLP) in this study is defined as low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L (130 mg/dL) or non-LDL-C ≥ 4.1 mmol/L (≥ 160 mg/dL). The NHANES database provides various methods for estimating LDL-C. We selected the results obtained using the National Institutes of Health (NIH) Equation 2 to reduce the impact of missing values. The NIH-2 equation was developed by Sampson *et al.* [20] from the National Institutes of Health in January 2020. Although the NIH-2 equation has not been as rigorously validated as the Friedewald or Martin-Hopkins equations, it still provides diagnostic utility [20].

2.5 NAFLD and MASLD

Nonalcoholic Fatty Liver Disease (NAFLD) and Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) were included in this study because their pathophysiological processes intersect with metabolic abnormalities. Liver ultrasound transient elastography was conducted by FibroScan® 502 V2 Touch device (Echosens, Paris, France) equipped with medium (M) or extra-large (XL) probes. Personnel training, standardized operating procedures, and other methods were used to ensure data quality (Liver

Ultrasound Transient Elastography Procedures Manual). Fatty liver was defined as a median controlled attenuation parameter (CAP) greater than 274 dB/m under vibration controlled transient elastography (VCTE) examination [21]. The definition of NAFLD in this study follows the criteria set by the American Association for the Study of Liver Disease, which excludes large-scale hepatitis, heavy alcohol consumption, and other potential causes of fatty liver. Heavy alcohol consumption is defined as an average intake of >60 g/day for males or >40 g/day for females. To reflect the pathogenesis of NAFLD more accurately, the international consensus renamed it MASLD in 2020 [22]. In addition to the original NAFLD criteria, MASLD includes descriptions of metabolic risk factors as follows [23]:

- BMI ≥ 25 kg/m² (23 Asia) OR waist circumference (WC) >94 cm (male) 80 cm (female) OR ethnicity adjusted equivalent;
- Fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) OR 2-hour post-load glucose levels ≥ 7.8 mmol/L (≥ 140 mg/dL) OR HbA1c $\geq 5.7\%$ (39 mmol/L) OR type 2 diabetes OR treatment for type 2 diabetes;
- Blood pressure $\geq 130/85$ mmHg OR specific antihypertensive drug treatment;
- Plasma triglycerides ≥ 1.70 mmol/L (150 mg/dL) OR lipid-lowering treatment;
- Plasma HDL-cholesterol ≤ 1.0 mmol/L (40 mg/dL) (male) and ≤ 1.3 mmol/L (50 mg/dL) (female) OR lipid-lowering treatment.

2.6 Covariates

Covariates were included to adjust the analysis, including age, sex (adjusted in the overall population analysis), race, marital status, education level, income level, smoking history, and alcohol history. Participants' ages were 20–39 years, 40–59 years, and ≥ 60 years. Race was classified into five groups: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other. Marital status was categorized as married or unmarried. Education level was divided into high school and high school or below. Smoking history was classified as having a history of smoking or not. Alcohol history was categorized as having a history of drinking or not.

2.7 Statistical analyze

The statistical analyses in this study considered the multi-stage probability sampling method used in the NHANES database and corrected the sample size using the minimum subset weight information. Differences in covariates were tested using the Chi-square test. The population characteristics are presented as unweighted case numbers and weighted percentages or means $\pm$ standard errors.

The exposure of interest was the PHQ-9 score, a measure of depressive symptoms. The outcomes were the presence of metabolic syndrome (MS) and its individual components. For the primary analysis, PHQ-9 scores were categorized into four groups based on well-established and clinically validated cut-offs to ensure clinical interpretability and comparability with existing literature: no depression (≤ 4), mild depression (5–9), moderate depression (10–14), and major depression

(≥ 15). To ensure the robustness of our findings and to explore the exposure-outcome relationship in greater detail, we supplemented our primary analysis by also treating the PHQ-9 score as a continuous variable modeled using restricted cubic splines (RCS) to capture any potential non-linear relationships, and by categorizing it into weighted quartiles for sensitivity analyses to test the consistency of associations across different modeling assumptions. For each outcome, we constructed three progressively adjusted models using weighted logistic regression: Model 1 (unadjusted); Model 2 (adjusted for age); and Model 3 (further adjusted for sex, race, marital status, education level, and poverty-income ratio), and a trend test was performed across the ordinal PHQ-9 categories to assess for dose-response relationships. In all multivariable models, the reference group was consistently defined as the no depression group (PHQ-9 score ≤ 4) and as the first weighted quartile (Q1).

Statistical analyses were performed using R software (version 4.0), and the survey package was used to adjust for the complex sample design of NHANES data. To account for multiple testing across the numerous metabolic outcomes examined, the False Discovery Rate (FDR) was controlled using the Benjamini-Hochberg procedure, applied separately within each subgroup and model. Therefore, the results of this study reflect the general status of the U.S. population aged 20 and older. Associations with an FDR-adjusted q -value < 0.05 were considered statistically significant.

3. Results

We excluded missing values and invalid samples in the NHANES 2017–2020 dataset, which had 15,560 samples. In the end, 3162 adults (202,474,260 after weighting) samples aged 20 and older were included (Fig. 1). Then, we applied weighting based on the minimum sample subset weight to form the final statistical analysis dataset (Supplementary Table 1).

The study initially included 15,560 participants. After screening for missing values in the metabolic syndrome-related indicators, 3162 participants with complete data were selected. Then, covariates were categorized, and metabolic syndrome and related diseases were diagnosed according to diagnostic criteria, as well as NAFLD and MASLD.

3.1 Characteristics of the study population based on PHQ-9 scores

We described the population based on depression score levels, dividing them into four groups: ≤ 4 points (no depression), 5–9 points (mild depression), 10–14 points (moderate depression), and ≥ 15 points (major or higher depression) (Supplementary Table 1). Among the included population, the most significant proportion was non-Hispanic White (63.7%), while other groups included Mexican Americans (8.8%), other Hispanics (6.8%), and non-Hispanics Black (10.9%). Although the proportions of different groups were relatively low, no significant ethnic differences were observed ($p = 0.09$). As reported in previous studies, sex was significantly associated with PHQ-9 scores ($p \leq 0.001$) (Fig. 2). As the PHQ-9 score increased, the

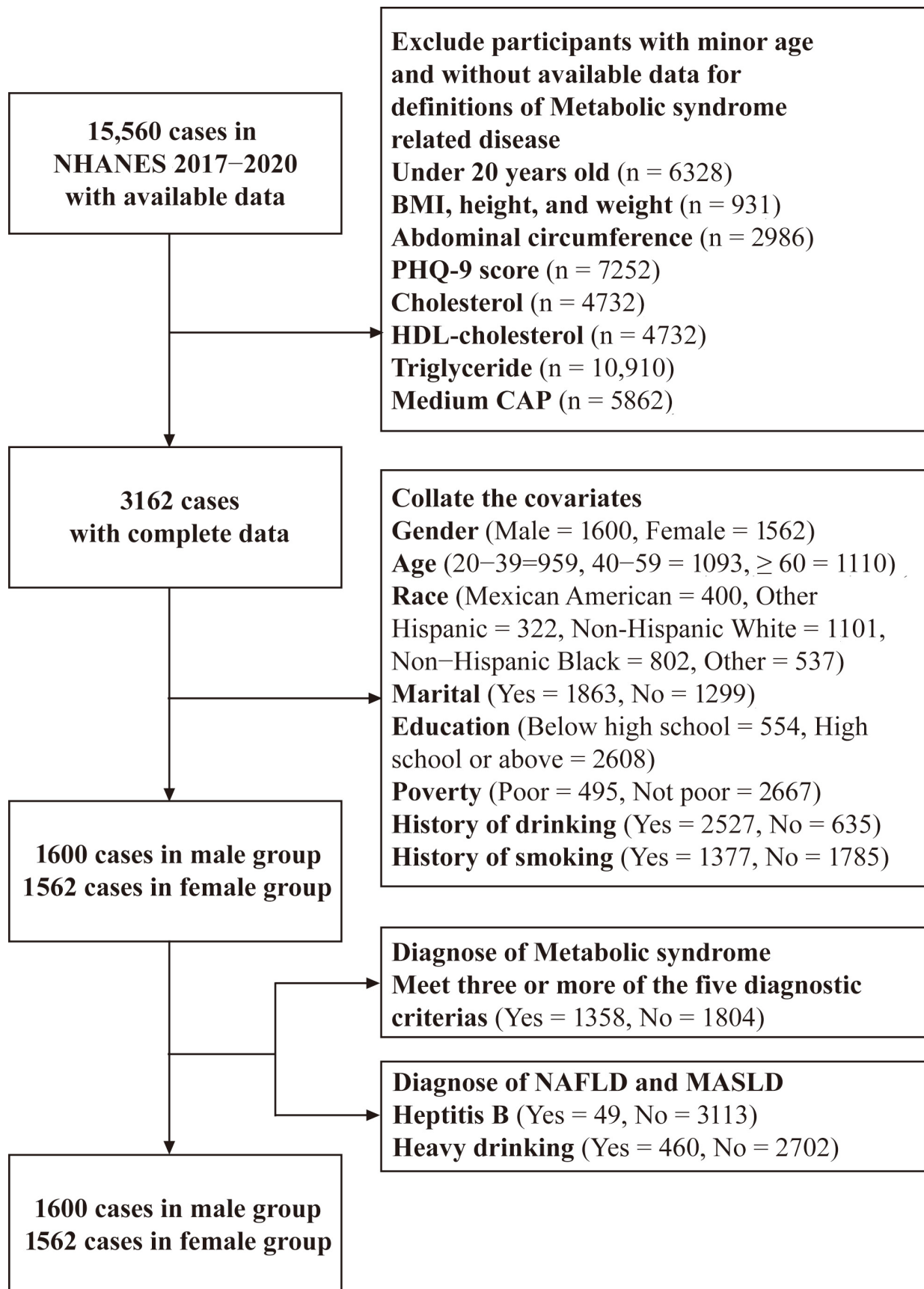


FIGURE 1. Flowchart of this study. NHANES: National Health and Nutrition Examination Survey; PHQ-9: Patient Health Questionnaire-9; HDL: high-density lipoprotein; CAP: controlled attenuation parameter; NAFLD: Non-Alcoholic Fatty Liver Disease; MASLD: Metabolic Dysfunction-Associated Fatty Liver Disease; BMI: body mass index.

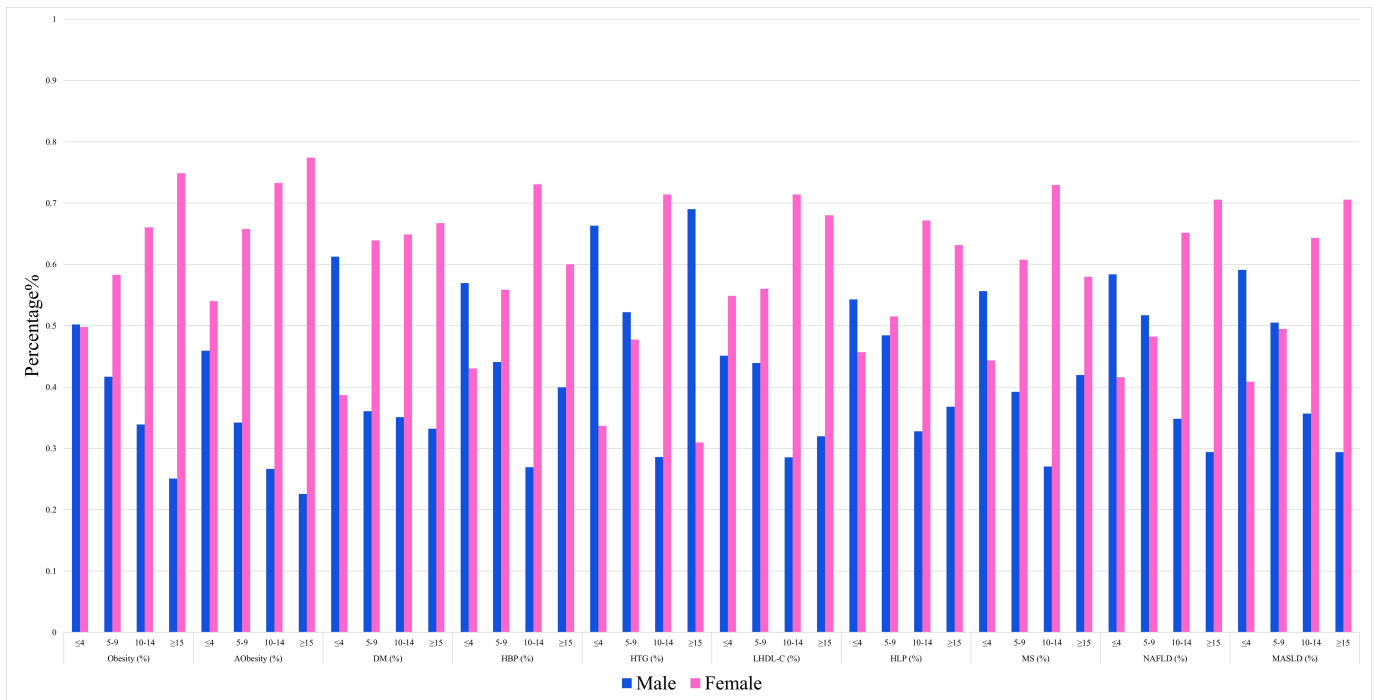


FIGURE 2. The proportion of metabolic dysfunctions related to sex in different levels of depression. For each metabolic dysfunctions, we grouped individuals based on depression levels and compared the proportions of different sex after weighting by their respective weights. DM: Diabetes Mellitus; HBP: Hypertension; HTG: Hypertriglyceridemia; LHDLC-C: Low HDL-cholesterol; HLP: Hyperlipidemia; MS: Metabolic Syndrome; NAFLD: Non-Alcoholic Fatty Liver Disease; MASLD: Metabolic Dysfunction-Associated Fatty Liver Disease.

proportion of females generally rose (≤ 4 : 47.2%, 5–9: 53.0%, 10–14: 67.9%, ≥ 15 : 64.1%). Among other covariates, marital status, education, poverty, smoking, and alcohol consumption showed significant differences between the groups. As PHQ-9 scores increased, the proportion of unmarried individuals, those with less than a high school education, non-drinkers, and non-smokers increased.

Among the outcome factors, several metabolic-related dysfunctions correlated with PHQ-9 scores. The median BMI and percentage of OB increased gradually with higher PHQ-9 scores ($29.20 \pm 6.79 \text{ kg/m}^2$, $30.40 \pm 7.61 \text{ kg/m}^2$, $31.08 \pm 8.34 \text{ kg/m}^2$, $32.27 \pm 8.16 \text{ kg/m}^2$, $p = 0.023$; 38%, 46.6%, 47%, 55.6%, $p = 0.013$). AOB, as part of MS, showed a similar trend. The median waist circumference and the rate of AOB in the study population also increased with higher PHQ-9 scores ($99.59 \pm 16.44 \text{ cm}$, $101.81 \pm 17.86 \text{ cm}$, $103.78 \pm 19.52 \text{ cm}$, $104.07 \pm 17.21 \text{ cm}$, $p = 0.058$; 53.5%, 61.1%, 67.0%, 69.7%, $p = 0.025$). Among other MS, HBP (34.2%, 44.3%, 47.7%, 49.8%, $p = 0.001$) and diabetes (14.7%, 17.3%, 24.6%, 14.8%, $p = 0.042$) showed significant correlations. Although LHDLC-C (26.6%, 28.1%, 36.3%, 39.3%, $p = 0.173$) and HTG (18.9%, 22.3%, 32.6%, 23.5%, $p = 0.073$) showed a trend of increasing with higher depression levels, they did not reach statistical significance. As a combined assessment of multiple indicators, MS (36.9%, 42.2%, 50.4%, 52%, $p = 0.056$) showed an increasing trend, with the significance level approaching the threshold.

As an outcome related to MS, HLP (49.6%, 50.4%, 56.4%, 49.8%, $p = 0.633$) showed a trend similar to that of MS but did not reach statistical significance. In addition, NAFLD (33.7%,

43.9%, 36.9%, 31.9%, $p = 0.036$) and MASLD (33.2%, 42.8%, 36.1%, 31.9%, $p = 0.053$) both showed significant or nearly significant trends across the groups as interconnected concepts, with their prevalence following a similar pattern of increase and decrease.

Overall, BMI, OB, AOB, HBP, NAFLD, and MASLD were significantly associated with depression levels. Among these, BMI, OB, AOB, and HBP showed a positive correlation with depression severity. Although NAFLD and MASLD also demonstrated significant associations, the highest prevalence of these conditions was observed in patients with mild to moderate depression. In contrast, their prevalence decreased in patients with major levels of depression.

3.2 Categorical variable analysis

In the categorical analysis utilizing established clinical thresholds, PHQ-9 scores were classified into four groups: ≤ 4 (no depression, reference), 5–9 (mild), 10–14 (moderate), and ≥ 15 (major). After FDR correction for multiple comparisons, analysis of the entire population revealed specific and robust associations between depression severity and metabolic dysfunctions in the fully adjusted model. HBP demonstrated the most consistent association, with risk significantly elevated in both the moderate and major depression groups (moderate: OR: 2.23, 95% CI: 1.15–4.30, $Q = 0.021$; major: OR: 2.76, 95% CI: 1.46–5.21, $Q = 0.008$).

NAFLD risk was significantly elevated, specifically in the mild depression group (OR: 1.65, 95% CI: 1.13–2.40, $Q = 0.039$). A suggestive but non-significant trend was observed for MASLD in the same group (OR: 1.60, 95% CI: 1.10–2.35,

Q = 0.057).

Notably, several nominally significant associations based on *p*-values were attenuated after FDR correction. This includes the elevated risk for DM in the moderately depressed group (OR: 2.33, 95% CI: 1.48–3.68, Q = 0.003), the increased risk for HTG in the same group (OR: 2.77, 95% CI: 1.2–6.39, Q = 0.06), and the elevated risk for MS in both the moderate and major groups (Moderate OR: 1.99, 95% CI: 1.17–3.38, Q = 0.023; Major OR: 2.27, 95% CI: 1.21–4.26, Q = 0.023). The risk of AOB also showed no significant individual associations after correction in model 3 (**Supplementary Table 2**).

Sex-stratified analyses revealed that the metabolic sequelae of depression were markedly different between males and females. In females, the phenotype of metabolic dysfunction was characterized primarily by adiposity-based and hypertensive risks. Specifically, AOB demonstrated a significant susceptibility. females with major depression had 3.5-fold greater odds of AOB compared to those without depression (OR: 3.46, 95% CI: 1.22–9.83, Q = 0.035). A significant increase in risk was also present even in the mildly depressed group (OR: 1.83, 95% CI: 1.11–3.00, Q = 0.035). This was complemented by a significant association between moderate depression and HBP (OR: 2.75, 95% CI: 1.27–5.94, Q = 0.042). Furthermore, it was also found that the incidence of DM was statistically significant in the moderate depression group (OR: 2.45, 95% CI: 1.22–4.93, Q = 0.048) (**Supplementary Table 3**).

Among males, the pattern of metabolic vulnerability was distinct and highly specific. After FDR correction, significant associations were concentrated almost exclusively in the major depression group and were characterized by lipid metabolism and hypertension risks. The most significant findings were 3.5-fold greater odds of HTG (OR: 3.53, 95% CI: 1.37–9.10, Q = 0.039) and a more than 4.8-fold greater odds of MS (OR: 4.83, 95% CI: 2.26–10.31, Q = 0.003) in the major depressed group. HBP risk was also significantly and markedly elevated in this group across models (Model 3 OR: 4.23, 95% CI: 1.80–9.98, Q = 0.009) (**Supplementary Table 4**).

To explore dose-response relationships using PHQ-9 quartiles, we found that participants in the highest quartile (Q4) had significantly higher odds of multiple metabolic dysfunctions after FDR correction in fully adjusted models. These included HTG (OR: 2.11, 95% CI: 1.45–3.09, Q = 0.003), DM (OR: 1.97, 95% CI: 1.48–2.61, Q = 0.003), HBP (OR: 1.94, 95% CI: 1.34–2.82, Q = 0.006), MS (OR: 2.03, 95% CI: 1.38–2.99, Q = 0.006), NAFLD (OR: 2.04, 95% CI: 1.46–2.85, Q = 0.003), MASLD (OR: 1.95, 95% CI: 1.4–2.73, Q = 0.003), OB (OR: 1.73, 95% CI: 1.24–2.41, Q = 0.012), AOB (OR: 1.81, 95% CI: 1.30–2.51, Q = 0.006), and HLP (OR: 1.36, 95% CI: 1.07–1.73, Q = 0.003). Associations for LHDLC were not significant after correction (**Supplementary Table 5**).

Sex stratified analysis revealed distinct metabolic risk patterns in females. In fully adjusted models, the highest depression quartile (Q4) showed a significant association only with HBP (OR: 2.02, 95% CI: 1.23–3.32, Q = 0.027). Other associations that were nominally significant based on *p*-values did not survive FDR correction, including AOB (OR: 2.14, 95% CI: 1.10–4.19, Q = 0.087), DM (OR: 1.78, 95% CI: 1.08–2.93, Q = 0.041), OB (OR: 1.60, 95% CI: 1.02–2.50, Q = 0.12), HTG (OR: 2.04, 95% CI: 1.06–3.90, Q = 0.066), and MS (OR:

1.75, 95% CI: 0.94–3.26, Q = 0.219) (**Supplementary Table 6**).

In contrast, male participants exhibited a distinct metabolic risk pattern. After FDR correction, the third depression quartile (Q3) showed significant associations with HTG (OR: 1.88, 95% CI: 1.34–2.64, Q = 0.003), AOB (OR: 2.18, 95% CI: 1.24–3.81, Q = 0.01), NAFLD (OR: 2.03, 95% CI: 1.21–3.43, Q = 0.017), MASLD (OR: 2.03, 95% CI: 1.22–3.39, Q = 0.015), and MS (OR: 2.62, 95% CI: 1.37–5.02, Q = 0.021) in fully adjusted models. The highest quartile (Q4) demonstrated significant associations with HTG (OR: 1.66, 95% CI: 1.06–2.62, Q = 0.045), HBP (OR: 2.07, 95% CI: 1.34–3.19, Q = 0.009), NAFLD (OR: 2.42, 95% CI: 1.46–4.01, Q = 0.006), and MASLD (OR: 2.22, 95% CI: 1.44–3.42, Q = 0.003) (**Supplementary Table 7**).

3.3 Continuous variable analysis

PHQ-9 scores were treated as a continuous variable to analyze various outcomes, aiming to observe the dose-response relationship between increasing PHQ-9 scores and the outcomes. After weighting the dataset and coordinating all the covariates, we sequentially plotted restricted cubic spline (RCS) curves to examine the relationship between PHQ-9 scores and the outcomes. In this section and the following ones, we performed additional subgroup analyses based on sex.

Following results were observed through the RCS curve: OB showed a similar trend in both male and female groups. The point of change in the OR was found in the 0–5 range, and the overall OR increased gradually with higher PHQ-9 scores (A: $p < 0.001$, p for nonlinear (NLP) = 0.01; male: $p < 0.001$, NLP = 0.056; female: $p < 0.001$, NLP = 0.182). However, for AOB, the RCS curve suggested that females seemed to have a higher OR compared to males, with the overall OR trend after the point of change being higher in the female group (A: $p < 0.001$, NLP = 0.001; male: $p < 0.001$, NLP = 0.009; female: $p < 0.001$, NLP = 0.058). In other metabolic syndrome-related diseases, the trend for HTG was similar between the male and female groups, with the overall OR increasing as PHQ-9 scores rose (A: $p < 0.001$, NLP = 0.031; male: $p < 0.001$, NLP = 0.146; female: $p < 0.001$, NLP = 0.028). For LHDLC, while the general population had a point of change between the 10–15 depression score range (A: $p < 0.001$, NLP = 0.006), the end of change for males was in the 0–5 score range (male: $p = 0.022$, NLP = 0.624), while for females it was in the 10–15 range (female: $p = 0.195$, NLP = 0.139). In the analysis of diabetes, both the overall population and the male-female groups showed significant differences (A: $p < 0.001$, NLP = 0.019; male: $p = 0.043$, NLP = 0.13; female: $p = 0.003$, NLP = 0.063). In the analysis with HBP as the outcome, the situation differed slightly: the risk of HBP was much higher in the female group ($p < 0.001$, NLP = 0.001) compared to the male group ($p \leq 0.001$, NLP = 0.007), which led to a higher overall HBP risk in the entire population ($p < 0.001$, NLP < 0.079).

As a result of multiple indicators combined, MS showed a positive correlation with PHQ-9 scores across all groups (A: $p < 0.001$, NLP < 0.001; male: $p < 0.001$, NLP = 0.004; female: $p < 0.001$, NLP = 0.17). Both NAFLD (A: $p < 0.001$,

NLP < 0.001; male: $p < 0.001$, NLP < 0.001; female: $p = 0.009$, NLP = 0.04) and MASLD (A: $p < 0.001$, NLP < 0.001; male: $p < 0.001$, NLP < 0.001; female: $p = 0.014$, NLP = 0.063) showed similar patterns. The first turning point for both was in the 0–5 group, and the second was in the 15–20 group. This means that, compared to those without depression or with major depression, patients with mild, moderate, and major depression have a higher risk of developing these conditions (Fig. 3).

4. Discussion

In this study led by the Centers for Disease Control and Prevention (CDC), we observed that PHQ-9 scores were associated with various metabolic Dysfunction, with notable differences between male and female subgroups. Specifically, we found that as depression severity increased, the proportion of females affected also gradually rose. Furthermore, females appeared to be more susceptible to conditions such as DM, HBP, OB, and AOB compared to males. These sex-specific differences highlight the need for tailored approaches to managing metabolic Dysfunction in individuals with depression, particularly among females.

As a common mental disorder, the prevalence of depression has been increasing over the past 20 years. From 1990 to 2019, the global incidence of major depressive disorder increased by 59.1% [24]. There are several definitions of MS, with the most widely used one being the standard proposed by the Third Report of the National Triglyceride Education Program (NCEP) Adult Treatment Panel (ATP III). According to this definition, MS is diagnosed when three conditions are met: AOB, elevated triglycerides, low HDL-cholesterol, high blood pressure, or elevated blood glucose.

Epidemiological studies in the past have suggested a link between depression and metabolic syndrome-related diseases. As early as 1981, R.S. Nathan and colleagues reported that insulin resistance was present in depressed patients, with some showing signs of insulin resistance during their illness [25]. Since then, researchers have explored the specific relationship between the two conditions. For example, in 2003, Albert J. Stunkard and others conducted a detailed review of the link between OB and depression, proposing a model that included moderating variables to identify the confounding effects of these factors [26]. In 2024, Weida Qiu discovered through the China Health and Retirement Longitudinal Study (CHARLS) cohort that there is a significant positive correlation between depression and hypertension among adults over the age of 45 [27]. Bruno Pinto and others reviewed the connection between depression and lipid metabolism disorders, summarizing the relationship between depression and lipid metabolism and suggesting that lipid profiles may become a future tool for predicting depression [28].

Although the exact mechanisms are unclear, epidemiological studies have revealed a relationship between depression and metabolic syndrome-related diseases, moreover, there is a harmful bidirectional interaction between these conditions, which may contribute to the development of complications like cardiovascular disease, ultimately increasing mortality [29]. Therefore, it is crucial to clarify the specific epidemiological

characteristics of these conditions, especially in public health.

In this study, we analyzed cross-sectional data from 2017 to 2020, finding that depression is linked to various health outcomes. At baseline, individuals with moderate or major depression were more likely to be female, aged 20–39, non-Hispanic White, unmarried, highly educated, and in good economic conditions. However, as depression severity increased, the proportion of those with lower education and in poverty also rose. We identified significant dose-response relationships between depression and components of MS, including OB, AOB, HTG, LHDL-C, HBP, NAFLD, and MASLD.

Subgroup analyses by sex revealed pronounced and distinct patterns of association between depression severity and metabolic dysfunction, underscoring the critical effect modifier role of sex. These patterns were consistently observed across both clinical severity categories and data-driven quartile analyses, reinforcing the robustness of our findings.

In females, the metabolic risk profile was primarily characterized by DM and HBP. A significant association with AOB was also observed specifically in the moderate depression group. Notably, several associations that were nominally significant based on p -values, particularly those related to OB and HTG, did not survive FDR correction. This refined pattern suggests that females with depression are prone to developing a metabolic phenotype centered on adiposity and blood pressure regulation, underscoring the importance of monitoring these parameters.

In contrast, male patients exhibited a distinct severity-dependent risk pattern that was most accurately captured by quartile-based analysis. While both analytical approaches confirmed the concentration of metabolic risk in more severely depressed males, the quartile method revealed both a broader range and stronger magnitude of associations, particularly for hepatic and cardiovascular outcomes. The most pronounced FDR-corrected risks emerged in the highest depression quartile (Q4), with markedly elevated odds for HTG (OR: 1.66, 95% CI: 1.06–2.62, $Q = 0.045$), HBP (OR: 2.07, 95% CI: 1.34–3.19, $Q = 0.009$), NAFLD (OR: 2.42, 95% CI: 1.46–4.01, $Q = 0.006$), and MASLD (OR: 2.22, 95% CI: 1.44–3.42, $Q = 0.003$). Meanwhile, Q3 also has a significantly increased risk of metabolic disorders like HTG (OR: 1.88, 95% CI: 1.34–2.64, $Q = 0.003$), AOB (OR: 2.18, 95% CI: 1.24–3.81, $Q = 0.01$), NAFLD (OR: 2.03, 95% CI: 1.21–3.43, $Q = 0.017$), MASLD (OR: 2.03, 95% CI: 1.22–3.39, $Q = 0.015$), and MS (OR: 2.62, 95% CI: 1.37–5.02, $Q = 0.021$) in fully adjusted models.

This study demonstrates fundamental sex differences in the metabolic consequences of depression, which are optimally captured by different analytical approaches. In females, depression-associated metabolic risk was most salient at the clinical threshold for moderate severity, manifesting primarily as a phenotype centered on abdominal obesity and hypertension. In males, metabolic risk exhibited a clear, progressive dose-response relationship with depression severity, which was most precisely captured by quartile-based analysis. Males in the highest depression quartile demonstrated markedly elevated risks encompassing the full spectrum of metabolic dysfunction, including hypertension, hypertriglyceridemia, metabolic syndrome, and fatty liver

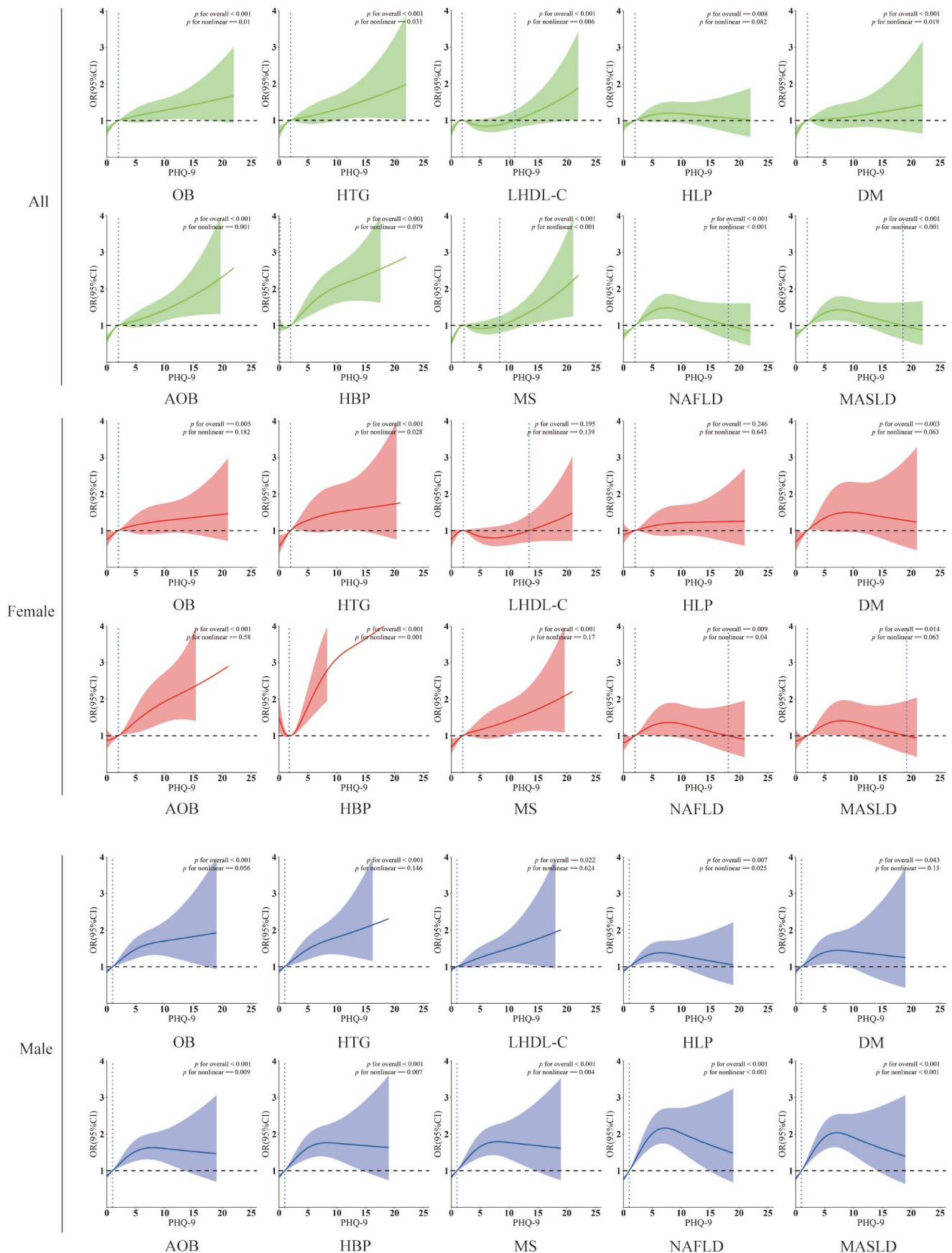


FIGURE 3. The restricted cubic spline curve for depression and metabolic dysfunctions after applying weighted data. OB: Obesity; HTG: Hypertriglyceridemia; LHDLC: Low HDL-cholesterol; DM: Diabetes Mellitus; HLP: Hyperlipidemia; AOB: Abdominal Obesity; HBP: Hypertension; MS: Metabolic Syndrome; NAFLD: Non-Alcoholic Fatty Liver Disease; MASLD: Metabolic Dysfunction-Associated Fatty Liver Disease; PHQ-9: Patient Health Questionnaire-9.

diseases.

The varying susceptibility to diseases observed in depressed patients in our study seems to be caused by a combination of factors such as biological, cultural, lifestyle, environmental, social status, and economic factors. The diversity of these multiple factors is associated with different levels of disease susceptibility in males and females under the influence of depression [30]. Among all the factors, physiological differences seem to be the crucial mechanism behind this phenomenon. The generalized metabolic vulnerability observed in females may be rooted in sex-specific neuroendocrine pathways. Estrogen-mediated fat distribution, favoring gluteal and femoral storage, is well-documented [29]. However, when coupled with depression, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may lead to excessive cortisol secretion, which promotes central adiposity, insulin resistance, and hypertension, which was the core components of the pattern we observed [31–33]. This mechanism may explain the strong associations with diabetes, obesity, and elevated blood pressure across all depression severity levels in females.

In contrast, we saw a clear dose-dependent pattern in males: rising depression scores were directly linked to higher metabolic risk. Preclinical models offer a potential explanation for this cumulative burden: sexual dimorphism in the corticotropin-releasing factor (CRF) system [34–36]. The relative lack of certain CRF receptors in male brains [37] may impair neural circuits governing stress recovery, leading to a gradual accumulation of allostatic load. This building physiological dysregulation may drive a continuous sympathetic nervous system activation and inflammatory response, ultimately manifesting as the markedly elevated odds ratios we observed for conditions like hypertension, hypertriglyceridemia, and full metabolic syndrome in the highest depression quartile. Concurrently, behaviors more common in depressed males, such as frequently alcohol use, may explain the persistent risk for fatty liver disease observed across the severity spectrum.

Our findings highlight a critical gap identified in the systematic review by Baldini *et al.* [38]—namely, the paucity of studies conducting rigorous sex-stratified analyses. While prior work by Liaw [39] and Cai [40] established a general link between depression and metabolic dysfunction, our granular, severity-based approach reveals that these associations are not uniform across sexes. This divergence highlights the necessity of going beyond merely adjusting for sex as a covariate. The null sex interaction reported by Chourpiliadis *et al.* [41] may stem from methodological differences; their study assessed metabolic biomarkers as risk factors for subsequent mental disorders, whereas our cross-sectional analysis examined depression as a correlate of metabolic outcomes. This distinction in causal direction and analytical focus may account for the discrepant findings regarding sex effects.

The distinct, sex-specific metabolic patterns uncovered in our study necessitate a paradigm shift from a uniform approach to sex-tailored strategies in both the clinical management and future research of depression.

For clinical practice, our findings advocate for the implementation of sex-specific precision screening protocols. For females with depression, clinicians should prioritize regular

monitoring of blood pressure and waist circumference, particularly upon identification of moderate depression, as this clinical threshold marks a significant elevation in cardiometabolic risk. For males, metabolic screening should be guided by depression severity. All depressed males warrant vigilance, but those with more severe symptoms require comprehensive metabolic evaluation, including lipid profiling and blood pressure assessment. Given the strong and persistent association between depression and hepatic steatosis in males, routine evaluation of liver enzymes (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST)) should be considered across the severity spectrum. Future research should also note these sex-based metabolic differences.

5. Strengths and limitations of the study

Our study's strength lies in using a large, nationwide, multi-ethnic U.S. sample, which is both extensive and representative. We employed various methods, including a coordination model, to control for confounders and enhance data reliability. Additionally, we conducted a sex-specific analysis of metabolic disease risks in depressed patients, providing robust epidemiological evidence. This is the only known study using a nationally representative sample for sex-specific analysis in this context.

However, this study has several limitations that should be considered. First, the cross-sectional nature of the NHANES data precludes the establishment of causal relationships between depression and metabolic parameters. Second, although more recent NHANES cycles (*e.g.*, 2021–2023) are available, they lacked critical laboratory data (specifically on triglycerides) essential for defining MS. Consequently, we utilized the most recent cycle with complete data (2017–2020) to ensure validity, though this may affect the temporal generalizability of our findings. Third, despite adjusting for a comprehensive set of covariates, residual confounding from unmeasured factors (*e.g.*, dietary habits, medication use) remains possible. Fourth, depression was assessed using the PHQ-9, a well-validated screening tool; however, it cannot substitute for a formal clinical diagnosis and may not capture the full spectrum of depression severity. Finally, the diagnoses of NAFLD and MASLD were based on non-invasive transient elastography rather than the gold standard of liver biopsy, which might influence diagnostic accuracy. Future prospective studies with longitudinal designs, more precise measurements, and additional biomarkers are warranted to confirm our findings and explore the underlying mechanisms.

6. Conclusions

In conclusion, our findings demonstrate a significant association between depression and an increased risk of metabolic dysfunction, with fundamental sex-specific patterns that are best captured through distinct analytical approaches. In females, depression-associated metabolic risk was most salient at the threshold of moderate severity, centering primarily on abdominal obesity and hypertension. In males, a clear dose-response relationship was observed, whereby metabolic risk—encompassing hypertension, hypertriglyceridemia,

full metabolic syndrome, and fatty liver diseases—escalated progressively with depression severity. Recognizing these distinct sex-specific manifestations will enable more precise prevention and tailored interventions, ultimately helping to mitigate the metabolic disease burden in individuals with depression.

ABBREVIATIONS

NHANES, National Health and Nutrition Examination Survey; RCS, Restricted Cubic Spline; OR, Odds ratio; FDR, False Discovery Rate; AOB, Abdominal Obesity; OB, Obesity; BMI, body mass index; HTG, Hypertriglyceridemia; LHDLC, Low HDL-cholesterol; HLP, Hyperlipidemia; HBP, Hypertension; DM, Diabetes Mellitus; MS, Metabolic Syndrome; NAFLD, Non-Alcoholic Fatty Liver Disease; MASLD, Metabolic Dysfunction-Associated Fatty Liver Disease; PHQ-9, Patient Health Questionnaire-9; NCHS, National Center for Health Statistics; CDC, Centers for Disease Control; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; MEC, Mobile Examination Center; CAPI, Computer Assisted Personal Interview; ATP III, Adult Treatment Panel III; FPG, Fasting plasma glucose; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; NIH, National Institutes of Health; M, medium; XL, extra-large; VCTE, vibration controlled transient elastography; WC, waist circumference; NLP, *p* for nonlinear; CDC, Centers for Disease Control and Prevention; NCEP, National Triglyceride Education Program; CHARLS, China Health and Retirement Longitudinal Study; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; LDL-C, low-density lipoprotein cholesterol; CAP, controlled attenuation parameter; PIR, Ratio of family income to poverty; TCHO, Total cholesterol.

AVAILABILITY OF DATA AND MATERIALS

The data used in this study were obtained from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 cycle. The NHANES data are publicly available and can be accessed through the official NHANES website (<https://www.cdc.gov/nchs/nhanes/index.htm>). All relevant data supporting the findings of this study are available from this publicly accessible database. Specific datasets and variables used in the analysis are available upon request, or they can be accessed directly from the NHANES website.

AUTHOR CONTRIBUTIONS

JDH and ZHZ—designed the research study. JDH, ZHZ and FMH—performed the research. BL—provided help and advice on methodology and validation. JDH—analyzed the data. JDH, ZHZ, FMH, YBH and YNS—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is a secondary analysis of data from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 cycle. The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB). Written informed consent was obtained from all NHANES participants. As our research utilized only de-identified public data, it was exempt from additional ethical approval. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and reported following the STROBE guidelines.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.jomh.org/files/article/1994307292344795136/attachment/Supplementary%20material.docx>.

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