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Original Article

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Bridging Three Years of Insights: Examining the Association Between Depression and Gallstone Disease

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Abstract

Background: Despite sharing common pathophysiological risk factors, the relationship between gallstones and depression requires further evidence for a clearer understanding. This study combines the National Health and Nutrition Examination Survey 2017 - 2020 observational data and Mendelian randomization (MR) analysis to shed light on the potential correlation between these conditions.

Methods: By analyzing the National Health and Nutrition Examination Survey 2017 - 2020 data through weighted multivariable-adjusted logistic regression, we examined the association between depression and gallstone risk. MR was subsequently applied, utilizing genetic instruments from a large genome-wide association study on depression (excluding 23andMe, 500,199 participants) and gallstone data (28,627 cases, 348,373 controls), employing the main inverse variance-weighted method alongside other MR methods to explore the causal relationship. Sensitivity analyses validated the study's conclusions.

Results: Among the 5,303 National Health and Nutrition Examination Survey participants, a significant association was found between depressive symptoms and increased gallstone risk (initial odds ratio (OR) = 2.001; 95% confidence interval (CI) = 1.523 - 2.598; P < 0.001), with the association persisting after comprehensive adjustments (final OR = 1.687; 95% CI = 1.261 - 2.234; P < 0.001). MR findings also indicated a causal link between genetically predicted depression and higher gallstone risk (OR = 1.164; 95% CI = 1.053 - 1.286; P = 0.003).

Conclusions: Depression is significantly associated with a higher risk of gallstones, supported by genetic evidence suggesting a causal link. These findings highlight the importance of considering depression in gallstone risk assessments and management strategies.

Keywords: Gallstone; Depression; National Health and Nutrition Examination Survey; Mendelian randomization analysis; Causality

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Introduction

Gallstone disease represents a major societal and economic burden [1] within the spectrum of gastrointestinal disorders, characterized by the formation of solid stones in the gallbladder [2]. Affecting approximately 20% of adults [3], a significant portion of these individuals suffer from symptomatic conditions, leading to substantial healthcare implications [4].

The etiology of gallstone disease is multifactorial, with risk factors encompassing obesity [5], type 2 diabetes [6], and certain lifestyle choices, including smoking, excessive alcohol consumption, and coffee intake [7]. Recent studies [8] have further highlighted a correlation between gallstone disease and mental health issues, notably depression, suggesting a complex interplay between physical and psychological health determinants.

Depression [9], characterized by persistent sorrow, diminished interest in activities, and cognitive impairments, poses a global health concern with increasing prevalence and association with various physical health disorders [10], including gastrointestinal and metabolic diseases [11]. Emerging evidence suggests that depression may influence metabolic processes, such as lipid metabolism and insulin sensitivity, which are key factors in gallstone formation [12]. Additionally, depression can affect gastrointestinal motility and bile acid secretion through stress-related pathways [13]. Therefore, exploring the potential causal relationship between depression and gallstone disease is of significant clinical interest.

Considering the constraints of traditional random controlled trials, including time and financial resources, this study seeks to leverage alternative research methodologies for causal inference. Utilizing Mendelian randomization [14], which employs genetic variation as instrumental variables, this research aims to estimate the causal effects of depression on gallstone disease. By integrating data from the National Health and Nutrition Examination Survey [15] 2017 - 2020 with a two-sample Mendelian randomization analysis, our study endeavors to elucidate the specific relationship between depression and

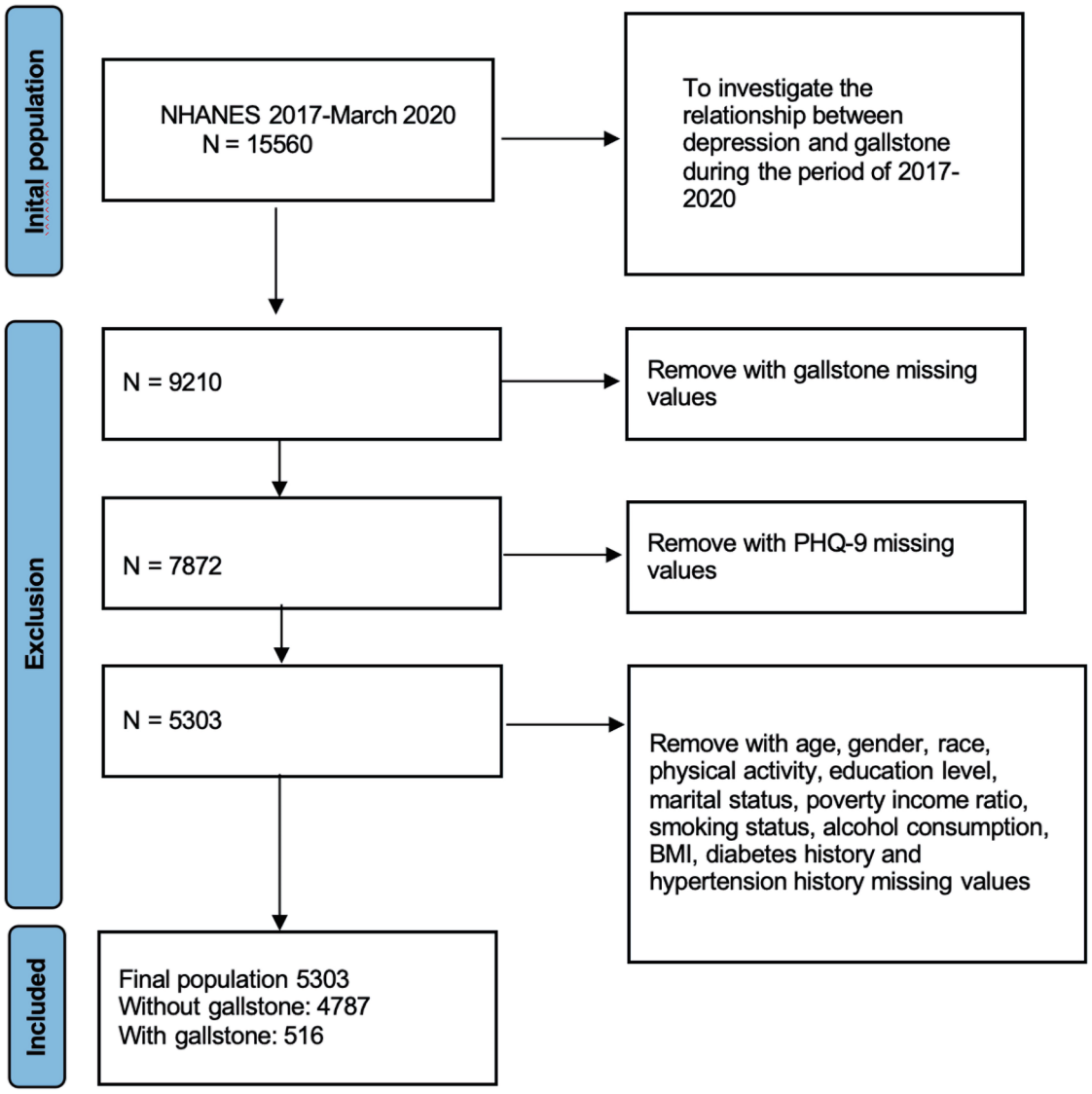

Figure 1. Flowchart on the stages of sample selection in this study. PHQ-9: Patient Health Questionnaire-9.

gallstones, thereby contributing to a deeper understanding of their interconnected pathophysiology [10, 15, 16].

Materials and Methods

Study population in the National Health and Nutrition Examination Survey dataset

The dataset for this study is freely available from the National Health and Nutrition Examination Survey database. Ethical approval for the National Health and Nutrition Examination Survey study protocols was granted by the National Center for Health Statistics (NCHS) Research Ethics Review Board. The use of deidentified, publicly accessible data negated the requirement for Institutional Review Board approval in this instance. This study was conducted in accordance with the ethical standards of the NCHS Research Ethics Review Board and complies with the Declaration of Helsinki.

Sample selection and exclusion criteria

Our study included adults aged 18 years and older from the National Health and Nutrition Examination Survey 2017 - 2020 cycles. Inclusion criteria required participants to have complete data on gallstone diagnosis, depressive symptoms assessed via the Patient Health Questionnaire-9, and key covariates. Exclusion criteria were: 1) missing data on gallstone status; 2) incomplete Patient Health Questionnaire-9 responses; 3) missing data on covariates such as age, gender, race, body mass index, smoking status, alcohol intake, physical activity, education level, poverty income ratio, hypertension, and diabetes history (Fig. 1).

Resulting sample composition

The exclusion process resulted in the elimination of 6,350 participants due to incomplete gallstone data, and an additional 1,438 were excluded due to inadequate Patient Health Questionnaire-9 questionnaire responses. A further exclusion of 2,569 individuals was necessitated by insufficient data on demographics and health status. This culminated in a final sample of 5,303 participants for analysis, comprising 4,787 individuals without gallstones and 516 with gallstones, providing a robust basis for investigating the relationship between depression and gallstone prevalence.

Assessment of depression and gallstone in the National Health and Nutrition Examination Survey

The assessment of depression and gallstones in the National Health and Nutrition Examination Survey study was conducted using validated instruments and criteria. Depression was evaluated using Patient Health Questionnaire-9 questionnaire [17], a nine-item depression screening tool with demonstrated reliability. The Patient Health Questionnaire-9 questionnaire quantifies the frequency of depressive symptoms [18] on a scale ranging from 0 (no incidence) to 3 (nearly every day). Participants scoring 10 or above were classified as having clinically significant depressive symptoms, with depressive symptoms coded as "0" for no (0 - 9 points) and "1" for yes (10 - 27 points) [19].

For gallstone assessment, the critical determinant was the response to survey question MCQ550, which inquires, "Has a doctor ever told you that you have gallstones?" As detailed in the National Health and Nutrition Examination Survey questionnaire documentation [20], an affirmative response to this question indicates the presence of gallstones. This self-reported, physician-diagnosed method has been validated in previous epidemiological studies where imaging confirmation is not feasible. For instance, one study [21] emphasized that self-reported gallstone disease is acceptable for large-scale studies, and it demonstrated good correlation between self-reported gallstones and ultrasound findings. Due to limitations in the National Health and Nutrition Examination Survey dataset, we were unable to differentiate between cholesterol and bilirubin gallstones. Therefore, our study analyzes gallstone disease as a whole without classifying it into subtypes. We recognize that this self-reported measure has limitations and does not constitute a comprehensive clinical assessment. Additionally, no imaging or other diagnostic procedures were directly performed as part of the National Health and Nutrition Examination Survey protocol for gallstone detection.

Other covariates used in the National Health and Nutrition Examination Survey

Our study additionally analyzed variables including age, smoking and alcohol use, gender, race, marital status, depressive symptoms, body mass index, physical activity (in metabolic equivalent of task (min/week)), education, poverty income ratio, and histories of hypertension and diabetes. We adjusted for socioeconomic factors such as smoking status, alcohol consumption, poverty income ratio, and education level, which are proxies for healthcare access and utilization. These adjustments help mitigate potential bias due to differential healthcare engagement.

Genome-wide association studies: single nucleotide polymorphism selection and analysis

Our methodology utilized genome-wide association studies to explore genetic variants, specifically single-nucleotide polymorphisms, associated with various traits and conditions. The data compilation, which adhered to ethical guidelines with participant consent, involved several key studies highlighted below: 1) Depression: We analyzed 8.1 million single-nucleotide polymorphisms in 500,199 individuals of European ancestry, excluding 23andMe data, to identify 102 genetic mutations linked to depression, emphasizing the prefrontal cortex's role [22]; 2) Gallstones: We focused on genetic factors affecting gastrointestinal motility by reviewing approximately 10.1 million single-nucleotide polymorphisms across 28,627 cases and 348,373 controls of European backgrounds, identifying key risk factors [23]; 3) Smoking and Drinking: We examined the genetic basis for smoking and drinking behaviors in over 1.23 million Europeans, assessing around 11.8 million single-nucleotide polymorphisms for predisposing genetic factors[24]; 4) Educational achievement: We investigated genetic influences on education level by analyzing about 8.1 million single-nucleotide polymorphisms in 1.1 million individuals, providing insights into the genetic contributions to academic success [25] (Supplementary Material 1, jocmr.elmerjournals.com).

Statistical analysis

We applied both analysis of variance and multivariate-adjusted logistic regression to investigate the association between depression and gallstone disease. Our analysis was structured around three progressively detailed models: model 1 (without any covariate adjustments), model 2 (adjusting for gender, age, and race), and model 3 (which further included adjustments for a comprehensive set of variables including education, marital status, poverty income ratio, body mass index, lifestyle factors (exercise, smoking, and alcohol consumption habits), and medical conditions like hypertension and diabetes). Outcomes were presented as odds ratios (ORs) or b coefficients, with a 95% confidence interval (CI), considering the National Health and Nutrition Examination Survey complex survey design.

To estimate the causal effects of depression on gallstone disease, we employed Mendelian randomization analysis. Mendelian randomization uses genetic variants as instrumental variables to infer causality between an exposure and an outcome, minimizing confounding and reverse causation inherent in observational studies [26]. This method leverages the random assortment of genes at conception, which serves as a natural experiment. We utilized a multivariable Mendelian randomization approach, focusing on the genetic predisposi-

tions to depression and their impact on gallstone risk. This method allowed us to refine causal inferences by adjusting for confounders among multiple exposure variables. Our primary analysis tool was the inverse variance-weighted method, complemented by four additional Mendelian randomization techniques (Mendelian randomization Egger regression, weighted median, Mendelian randomization pleiotropy residual sum and outlier, and analyses excluding palindromic and pleiotropic single-nucleotide polymorphisms) to validate findings and assess for biases such as pleiotropy. Significant heterogeneity and pleiotropy were addressed using weighted median and Mendelian randomization Egger methods, respectively, with a significance threshold set at $P < 0.05$. Mendelian randomization pleiotropy residual sum and outlier and leave-one-out analyses were also performed to ensure the robustness of our results. These analyses were conducted within the R 4.1.2 software environment.

All in all, given that our primary analysis focused on a specific hypothesis testing the association between depression and gallstone disease, adjustments for multiple comparisons were not applied. In our main logistic regression analysis, we used a single primary outcome (gallstone disease) and a single primary exposure (depression), which does not necessitate correction for multiple comparisons. In the Mendelian randomization analysis, we used various methods to ensure robustness of the findings rather than conducting multiple independent tests. These methods are complementary approaches to assess the consistency of our results and are not treated as separate hypothesis tests requiring correction.

Results

Characteristics of the participants with and without gallstone

During the study period (2017 - 2020), a total of 5,303 persons from the United States having data on exposure factors (depression) and outcomes (gallstones) were eligible for analysis, with their key features listed in (Table 1). Among these participants, 516 were eligible for gallstone inclusion. The purpose of this descriptive analysis was to outline the demographics of the research population at the outset and to look for variations between the two groups that would impact the interpretation of the findings.

Several factors were considered in this analysis, including age; smoking status (smoking refers to smoking at least 100 cigarettes in life, then dichotomized to no (< 100 cigarettes or never smoking) and yes (> 100 cigarettes); alcohol intake (drinking refers to consuming four or more drinks a day in the past 12 months), and dichotomized to no (never drinking) and yes (one or more days drinking); gender; race; marital status; depressive symptoms; body mass index; physical activity (metabolic equivalent of task (min/week); education level; poverty income ratio; hypertension; and diabetes history. People with depressive symptoms, older adults, smokers (> 100 cigarettes), Mexican American, other Hispanic, non-Hispanic White females, obesity, hypertension, and diabetes history were more likely to develop gallstone disease than healthy controls, while those with high alcohol intake, non-Hispanic Black, other race, and never married people had a lower chance of developing gallstones (P value < 0.05).

Observational associations between depression and gallstone in the National Health and Nutrition Examination Survey

We adjusted for several covariates and further examined the link between gallstones and depressive symptoms. Model 1 did not include any adjustments, model 2 included adjustments for sex, age, and race, and model 3 was a multivariate model that included variables such as education, marital status, poverty income ratio, body mass index, physical activity, smoking status, alcohol use, history of diabetes, hypertension, among many others. Even after adjusting for all factors, we discovered a significant connection between gallstones and depressive symptoms in model 1, with an OR of 2.001 and a 95% CI of 1.523 to 2.598 (P value < 0.001). This indicates that gallstones are more than twice as likely to develop in people with depressive symptoms compared to those without these symptoms. After accounting for sex, age, and race, this link was still significant in model 2 (OR = 1.928; 95% CI = 1.455 to 2.528; P value < 0.001). The risk of gallstones in individuals with depressive symptoms was still significant in the more thorough model 3, even after additional potential confounders were considered (OR = 1.687; 95% CI = 1.261 to 2.234; P value < 0.001). However, the risk ratios decreased slightly when compared to models 1 and 2, which could be due to the other variables partially mediating the association between depressive symptoms and gallstones (Table 2).

Causal relationships between depression and gallstone risk in Mendelian randomization

This study utilized Mendelian randomization analysis with genetic tools identified through genome-wide association studies for depression. We derived F-statistics for each single nucleotide polymorphism by calculating effect sizes and standard errors for each genetic tool. By gathering the F-statistics from various genetic tools, we calculated an average F-statistic that demonstrated the strong explanatory capability of the chosen genetic tools (Supplementary Material 2, jocmr.elmerjournals.com).

We investigated the relationship between depression and gallstone disease using various Mendelian randomization techniques in our study. We employed several Mendelian randomization techniques, including inverse variance weighting, Mendelian randomization Egger regression, weighted median method, and Mendelian randomization pleiotropy residual sum and outlier. Our analysis focused on genetic variants (single-nucleotide polymorphisms) that were linked to depression but not influenced by gallstones. These methods were used to evaluate the relationship between depression and gallstones. They looked at factors like the OR, the 95% CIs, and P values to determine

Table 1. Characteristics of the Participants With and Without Gallstone

	Non-gallstone (4,787)	Gallstone (516)	Statistics	P value
Age (years)	47 (33, 62)	57 (43, 69)	205.455	< 0.001[a]
Smoker status			9.473	0.002[b]
No	2,841 (59.35%)	270 (52.33%)		
Yes	1,946 (40.65%)	246 (47.67%)		
Alcohol intake			8.504	0.004[b]
No	3,982 (83.18%)	455 (88.18%)		
Yes	805 (16.82%)	61 (11.82%)		
Gender			103.958	< 0.001[b]
Male	2,429 (50.74%)	140 (27.13%)		
Female	2,358 (49.26%)	376 (72.87%)		
Race			29.312	< 0.001[b]
Mexican American	502 (10.49%)	65 (12.60%)		
Other Hispanic	441 (9.21%)	55 (10.66%)		
Non-Hispanic White	1,725 (36.04%)	231 (44.77%)		
Non-Hispanic Black	1,291 (26.97%)	96 (18.60%)		
Another race	828 (17.30%)	69 (13.37%)		
Marital status			27.823	< 0.001[b]
Married/living with partner	2,813 (58.76%)	312 (60.47%)		
Widowed/divorced/separated	959 (20.03%)	139 (26.94%)		
Never married	1,014 (21.18%)	65 (12.60%)		
Depressive symptoms			26.935	< 0.001[b]
No	4,412 (92.17%)	441 (85.47%)		
Yes	375 (7.83%)	75 (14.53%)		
Body mass index			47.153	< 0.001[b]
< 30	3,040 (63.51%)	248 (48.06%)		
≥ 30	1,747 (36.49%)	268 (51.94%)		
Physical activity (metabolic equivalent of task (min/week))			22.817	< 0.001[b]
< 600	1,585 (33.11%)	225 (43.60%)		
≥ 600	3,202 (66.89%)	291 (56.40%)		
Education level			0.005	0.945[b]
≤ high school	664 (13.87%)	71 (13.76%)		
> high school	4,123 (86.13%)	445 (86.24%)		
Poverty income ratio	2.46 (1.26, 4.62)	2.24 (1.28, 4.27)	115.317	< 0.001[a]
Hypertension history			56.773	< 0.001[b]
Without hypertension	3,157 (65.95%)	254 (49.22%)		
With hypertension	1,630 (34.05%)	262 (50.78%)		
Diabetes history			53.902	< 0.001[b]
Without diabetes	4,095 (85.54%)	383 (74.22%)		
With diabetes	567 (11.84%)	120 (23.26%)		
Prediabetes	125 (2.61%)	13 (2.52%)		

Data were presented as median (interquartile range) or n (%). [a]*t*-test for continuous variables. [b]Pearson's Chi-squared test for categorical variables.

Table 2. Association Between Depressive and Gallstone

	Gallstone, OR (95% CI), P value		
	Model 1	**Model 2**	**Model 3**
Without depressive symptoms	Reference	Reference	Reference
With depressive symptoms	2.001(1.523, 2.598), P < 0.001	1.928 (1.455, 2.528), P < 0.001	1.687 (1.261, 2.234), P < 0.001

Model 1 did not include any adjustments. Model 2 was adjusted for: gender, age, and race. Model 3 was adjusted for: gender, age, race, education level, marital status, poverty income ratio, body mass index, physical activity, smoking status, alcohol intake, diabetes history and hypertension history. OR: odds ratio; CI: confidence interval.

the strength and statistical significance of the association.

The study discovered several important results. The inverse variance weighting method utilized 87 single-nucleotide polymorphisms and resulted in a moderate positive correlation between depression and gallstones (OR of 1.164, P value of 0.003). The Mendelian randomization Egger regression method also utilized 87 single-nucleotide polymorphisms. However, its 95% CI ranged from 0.684 to 2.169, with a P value of 0.5. This suggests that there might not be any instrumental variable nullity or horizontal heterogeneity. Both the weighted median method and Mendelian randomization pleiotropy residual sum and outlier (after removing three outliers) indicated a positive link between depression and gallstones. Furthermore, even after removing palindromic single-nucleotide polymorphisms, the data still revealed a significant correlation between depression and an increased risk of gallstones. Based on the findings, it appears that there is a potential link between depression and an increased likelihood of developing gallstone disease (Table 3).

In addition, we applied multivariable Mendelian randomization to display three models, each evaluating the individual impact of depression on the risk of gallstones. These models were adjusted independently for various confounding variables. In the forest plot, the dots represent the OR of the impact of depression on the risk of gallstone disease in each model. The horizontal line represents the 95% CI. If the 95% CI contains 1, it indicates that there is no statistically significant association between depression and gallstone risk.

Our analysis revealed a clear and positive link between depressed mood and the risk of gallstone disease. In our stratified analysis by healthcare utilization levels, the association between depression and gallstone disease remained positively significant across all strata (smoking status: OR = 1.13, 95% CI: 1.01 - 1.25; alcohol intake: OR = 1.21, 95% CI: 1.09 - 1.34; educational attainment: OR = 1.14, 95% CI: 1.03 - 1.27), suggesting that the relationship is not solely driven by differences in healthcare engagement (Fig. 2).

To ensure that the main results of our Mendelian randomization analysis were robust, we conducted a leave-one-out study sensitivity analysis. By using this method, we can determine how various single-nucleotide polymorphisms affect the likelihood of a causal link existing between depression and gallstone disease. Eliminating each single-nucleotide polymorphism one at a time allows us to observe how it changes the estimates and statistical significance. When a single-nucleotide polymorphism is removed from the equation, the table shows the expected outcomes (such as ORs) along with their 95% CIs and the corresponding P values. The statistical results show that most of the points are very close to the center line. This means that no single single-nucleotide polymorphism has a significant effect on the causal estimate, which makes the overall estimate more reliable. The single-nucleotide polymorphisms utilized in our Mendelian randomization analysis are associated with genes implicated in neurobiological and metabolic pathways. For example, sirtuin 1 is involved in mitochondrial function and energy regulation, potentially linking depression to metabolic disturbances that contribute to gallstone formation. Understanding the functions of these single-nucleotide polymorphisms provides biological plausibility to our findings and suggests potential mechanisms underlying the observed association (Fig. 3 and Supplementary Material 2, jocmr.elmerjournals.com).

Discussion

The intersection between mental and physical health is a growing area of interest within the medical and scientific commu-

Table 3. Causal Effects of Depression on Gallstone Disease

Exposure	Method	nSNP	OR (95% CI)	P value
Depression	Inverse variance weighted	87	1.164 (1.053 - 1.286)	0.003
	MR Egger	87	1.218 (0.684 - 2.169)	0.5
	Weighted median	87	1.142 (1.022 - 1.277)	0.019
	MR-PRESSO (3 outlier-corrected)	84	1.113 (1.020 - 1.215)	0.018
	Excluding palindromic SNPs	82	1.180 (1.064 - 1.308)	0.002
	Excluding pleiotropic SNPs	63	1.143 (1.023 - 1.278)	0.018

MR: Mendelian randomization; SNP: single-nucleotide polymorphism; OR: odds ratio; CI: confidence interval; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier.

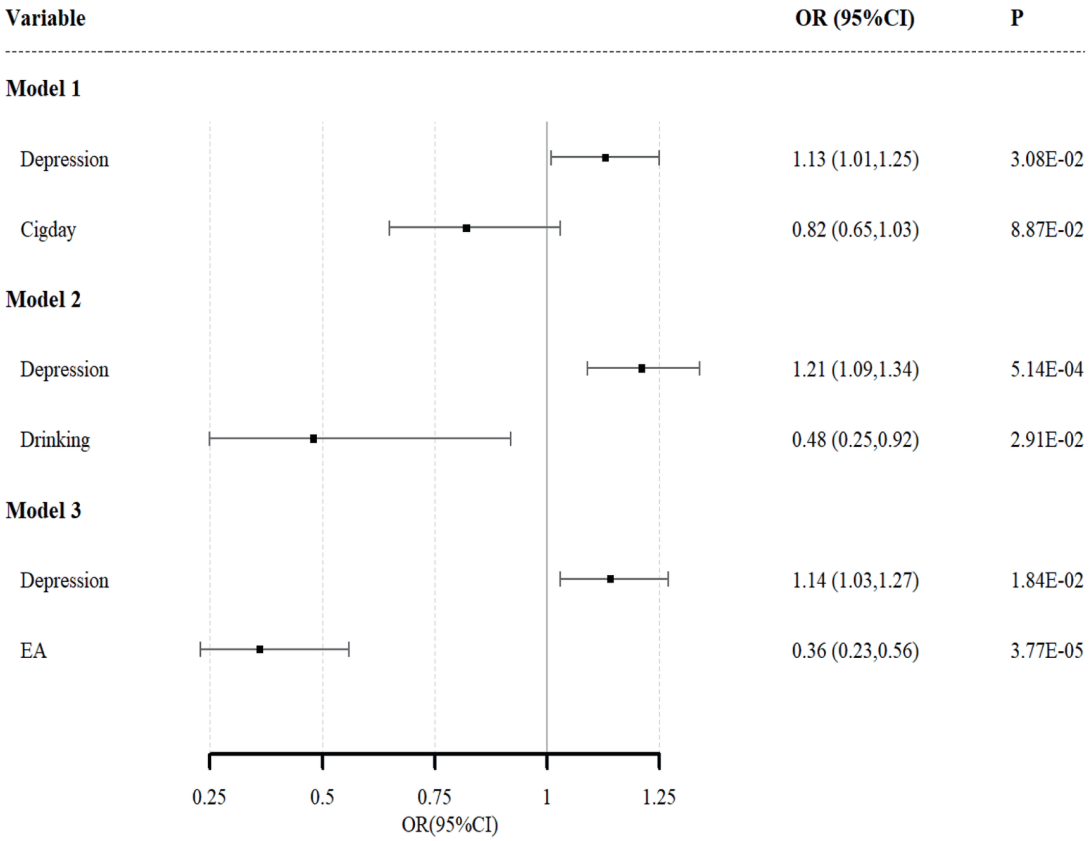

Figure 2. Independent effect of depression on the risk of gallstone disease using multivariable Mendelian randomization analysis. Model 1: independent effect of depression on gallstone disease after adjusting for cigarettes per day. Model 2: independent effect of depression on gallstone disease after adjusting for drinking. Model 3: independent effect of depression on gallstone disease after adjusting for education attainment (EA). Cigday: Heaviness of smoking was measured with cigarettes per day; OR: odds ratio; CI: confidence interval.

nities, especially as emerging evidence continues to support the intricate links between psychological states and physical health outcomes. This study contributes significantly to this body of knowledge, highlighting the association and potential causal relationship between depression and the risk of gallstone disease. This consistency with recent scholarly work reinforces the strength and reliability of our findings across diverse methodologies and datasets.

For instance, a study by Ji et al [27] highlighted the epidemiological ties between metabolic disorders and psychiatric conditions, aligning with our observations on the depression-gallstone nexus. Similarly, research by Iob et al [28] provides evidence for the bidirectional influence of mental and physical health, supporting our Mendelian randomization findings. Furthermore, Smith et al [29] on the principles of Mendelian randomization underscores the validity of our approach in establishing causality between depression and gallstone disease, advocating for the robustness of integrating genetic data with observational research.

The observational data from National Health and Nutrition Examination Survey revealed that individuals with depressive symptoms had a significantly higher likelihood of developing gallstones [30], compared to those without depressive symptoms, even after adjusting for multiple covariates including lifestyle factors and comorbidities [31]. This association persisted across various models of adjustment, indicating a robust relationship.

Previous studies [2, 32] have highlighted the psychological stress and altered gastrointestinal motility associated with depression, which could exacerbate the risk of gallstone formation [3]. Furthermore, the impact of depression on lifestyle choices, such as physical inactivity and dietary habits, may contribute to the risk factors associated with gallstone disease [6, 8, 33].

The Mendelian randomization analysis further substantiates the observational findings by suggesting a causal relationship between genetically predicted depression and the risk of gallstone disease [23, 34]. This genetic approach helps overcome the limitations of observational studies by reducing confounding and reverse causality, providing more robust evidence of the relationship. The use of genetic instruments derived from large-scale genome-wide association study meta-analyses ensures the reliability and validity of the Mendelian randomization findings [22, 23], and we acknowledge that differential healthcare utilization could influence the likelihood of gallstone diagnosis. To address this, we adjusted for socio-

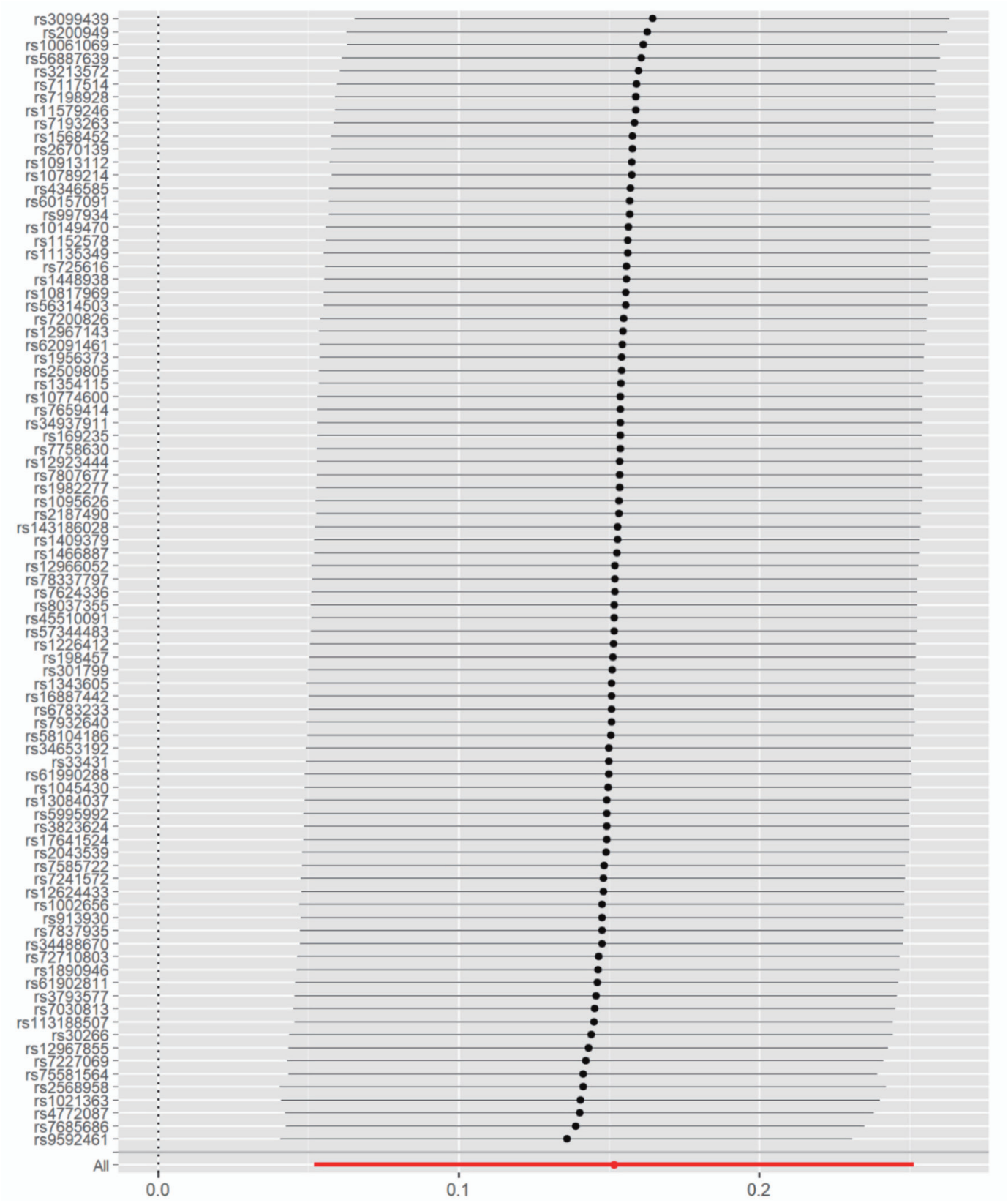

Figure 3. Results from the leave-one-out analysis which excluded each single nucleotide polymorphism to estimate the effects of depression-related traits on gallstone disease.

economic factors such as cigarettes per day, drinking, education level, as well as direct measures of healthcare engagement. Our sensitivity analyses indicated that the association between depression and gallstone disease remained significant after these adjustments, suggesting that the observed relationship is unlikely to be solely due to detection bias.

The elucidation of a link between depression and gallstone disease [35, 36] has important clinical implications. It underscores the necessity of holistic patient care, integrating mental health assessment and management into the treatment plan for patients at risk of or suffering from gallstone disease. Furthermore, these findings highlight the importance of interdisciplinary approaches to managing patients with gallstone disease, considering both physiological and psychological factors in treatment and prevention strategies [16].

A key advantage of our study is the dual-method approach that combines traditional epidemiological analysis with Mendelian randomization. Using data from the National Health and Nutrition Examination Survey 2017 - 2020 and Mendelian randomization, we discovered a significant link between depression and gallstone disease. Our findings from weighted logistic regression show that depressive symptoms significantly increase the risk of gallstones (OR: 1.687; $P < 0.001$). Mendelian randomization further supports the causal relationship between these conditions (OR: 1.164; $P = 0.003$). These results emphasize the importance of including mental health care in the management of gallstone disease.

The inverse association between alcohol use and gallstone disease observed in our study aligns with previous research suggesting that moderate alcohol consumption may reduce gallstone risk by enhancing bile flow and reducing cholesterol crystallization [37]. However, this finding should be interpreted with caution, and it is essential to consider the detrimental effects of excessive alcohol intake.

Furthermore, we acknowledge that this association could be influenced by other factors, including healthcare utilization patterns. The observed inverse relationship between alcohol use and gallstone disease may indeed be partially explained by differences in healthcare utilization. Individuals who report moderate alcohol consumption might represent a subset of the population more likely to engage in routine healthcare, potentially leading to earlier detection and management of risk factors for gallstone disease. Conversely, heavy alcohol users might be less likely to seek regular medical care, potentially resulting in underdiagnosis of gallstones in this group. We attempted to mitigate this potential confounding effect by adjusting for socioeconomic factors and healthcare utilization measures in our analysis. However, residual confounding cannot be ruled out entirely.

One limitation of our study is the reliance on self-reported physician diagnoses for gallstone disease, which may introduce misclassification bias. However, prior research indicates that self-reported gallstone disease has acceptable validity for epidemiological studies [21]. Given that gallstones often cause symptoms leading individuals to seek medical attention, we believe the impact of this bias on our findings is minimal.

The other is the inability to distinguish between cholesterol and bilirubin gallstones. Given that cholesterol stones are more prevalent in Western countries and are associated with metabolic factors that may be influenced by depression, our findings might predominantly reflect the risk related to cholesterol stones. Our reliance on self-reported, physician-diagnosed gallstone disease is a limitation of this study. While this approach is common in large-scale epidemiological studies, it may underestimate the true prevalence of gallstones, as asymptomatic cases might go undiagnosed. Future studies incorporating imaging techniques such as ultrasonography would provide a more accurate assessment of gallstone prevalence and could potentially strengthen our findings. Future studies with detailed gallstone classification are warranted to explore this aspect further.

While this study provides substantial evidence of an association between depression and gallstone disease, further research is needed to elucidate the underlying mechanisms. Further research needs to uncover the biological pathways linking depression to gallstone pathogenesis. Additionally, intervention studies focusing on the management of depression could provide insights into potential reductions in gallstone disease risk, offering a new avenue for prevention and treatment strategies.

Supplementary Material

Suppl 1. Details on the characteristics of each included dataset.

Suppl 2. Characteristics of GWAS-identified depression-associated genetic instruments.

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The authors reported there is no funding associated with the work featured in this article.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Informed Consent

The study utilized data from the National Health and Nutrition Examination Survey (NHANES) database, where informed consent was obtained from all participants by the National Center for Health Statistics (NCHS). For the GWAS component, all genetic data were obtained from publicly available summary statistics where original studies obtained appropriate consent from participants.

Author Contributions

HZW drafted the initial manuscript and conducted the data analysis. SS and JYZ drafted and revised the manuscript. SHH provided guidance in manuscript and identified mistakes in the manuscript. All authors reviewed the final manuscript.

Data Availability

The dataset for this study is freely available from the National Health and Nutrition Examination Survey database (https://www.cdc.gov/nchs/National Health and Nutrition Examination Survey/index.htm). And data supporting the findings of this study are viewable within the article's figures and will be available in spreadsheet form from the corresponding author upon reasonable request.

Abbreviations

ANOVA: analysis of variance; BMI: body mass index; CI: confidence interval; Cigday: cigarettes per day; F-statistic: Fisher's statistic; GWAS: genome-wide association studies; IVW: inverse variance-weighted; MET: metabolic equivalent of task; MR: Mendelian randomization; MR Egger: Mendelian randomization Egger regression; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier; MVMR: multivariable Mendelian randomization; NCHS: National Center for Health Statistics; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9; PIR: poverty income ratio; SIRT1: sirtuin 1; SNP: single-nucleotide polymorphism

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