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Associations between monocyte to HDL-C ratio and lumbar bone mineral density in alcohol dependent individuals with depression

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Osteoporosis, a skeletal disorder that reduces bone density, is a significant health concern. Alcohol dependence, a chronic condition, exacerbates public health problems due to its widespread occurrence and association with various comorbidities, including depression. This study aims to explore the relationship between monocyte to high-density lipoprotein cholesterol ratio (MHR) and lumbar bone mineral density (BMD)in individuals with alcohol dependence and depression. From 2009 to 2018, 49,693 participants were enrolled, and after screening, the study included 2,055 individuals with alcohol-dependency and depression. In this study, multivariate regression analysis was employed to assess the association between monocyte to HDL-C ratio and lumbar bone mineral density. Additionally, we conducted interaction tests and subgroup analysis. The result showed a negative correlation between MHR and lumbar BMD, which remained significant even after adjusting for covariates. Individuals with less than a 9th-grade education showed a positive link with MHR, while those with a college degree or higher had a negative link. This relationship remained significant in the fully adjusted model. A U-shaped relationship between MHR and lumbar BMD was observed in individuals with a high school diploma/GED, after adjusting for various factors. The intricate correlation between MHR and lumbar BMD may suggest the presence of biological interplays and disparities in socioeconomic or behavioral aspects. This underscores the necessity for tailored public health strategies that cater to various educational demographics.

Keywords Osteoporosis, Alcohol-dependent, Depression, MHR, BMD

Osteoporosis, a systemic skeletal disorder marked by diminished bone mineral density (BMD), represents a substantial public health issue owing to its correlation with heightened fracture risk and diminished quality of life[1,2]. Simultaneously, alcohol dependence, a chronic relapsing condition, exacerbates public health problems due to its widespread occurrence and links to various comorbidities, including mental health disorders like depression[3]. Depression, frequently seen alongside alcohol use disorders, may alter bone metabolism through its effects on the neuroendocrine and immune systems. Studies indicate a complex relationship between depression and bone health, with evidence showing a link between depressive symptoms and reduced bone mineral density[4–6]. Previous research has demonstrated that depression elevates cortisol levels by activating the hypothalamic–pituitary–adrenal (HPA) axis, and that hypercortisolemia is a significant causal factor in the deterioration of bone health[7]. In addition, increased levels of inflammatory cytokines like interleukin-1β, interleukin-2, and interleukin-6 are found in depression and are linked to reduced bone mineral density[8]. The potential biological plausibility of this association encompasses the influence of depressive symptoms on physical activity, dietary consumption, and hormonal regulation, each of which is crucial for sustaining bone health. Moreover, the psychosocial stress associated with depression could trigger neuroendocrine and immune reactions that negatively affect the bone remodeling processes[9].

The detrimental impact of both alcohol dependence and depression on bone health is well-documented[10]. The monocyte to high-density lipoprotein cholesterol ratio (MHR) is an emerging biomarker that reflects systemic

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inflammatory status, which integrates two pathophysiological dimensions including monocytes which are pivotal mediators of innate immunity, promote pro-inflammatory responses, and HDL-C provides anti-inflammatory and antioxidant effects through vascular cholesterol clearance and the mitigation of atherosclerosis[11]. An elevated MHR indicates an imbalance skewed towards inflammation, which has recently been associated with dysregulation in bone metabolism. Mechanistically, chronic inflammation enhances osteoclast activation while suppressing osteoblast function, thereby accelerating bone resorption and reducing bone mineral density[12]. This phenomenon is particularly exacerbated in populations experiencing the dual challenges of alcohol dependence and depression. Alcohol-induced oxidative stress and depression-related hyperactivity of the HPA axis may synergistically intensify this inflammatory cascade. Consequently, MHR emerges as a promising indicator for elucidating the complex interplay between inflammation, addictive-metabolic disorders, and skeletal health, offering valuable clinical insights into the preservation of BMD.

Despite a growing body of evidence linking alcohol consumption, depression, and bone health, the specific function of the MHR within the context of lumbar BMD among individuals suffering from alcohol dependence and depression remains inadequately investigated.

The principal objective of this cross-sectional study is to scrutinize the correlation between MHR and lumbar BMD in a nationally representative cohort of individuals diagnosed with alcohol dependency and depression. The hypothesis under investigation suggests that an elevated MHR, serving as a marker of systemic inflammation, may exhibit an inverse relationship with lumbar BMD, thereby potentially pinpointing a modifiable risk factor for osteoporosis within this susceptible demographic. By illuminating the role of systemic inflammation within this framework, this study endeavors to augment the comprehension of the multifactorial determinants that influence bone health.

Materials and methods

Study design and participants

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive, ongoing, cross-sectional survey in the United States. It is designed to provide objective statistics on a range of health issues and to address emerging public health concerns. All data required for the research was collated from the five continuous NHANES cycles from 2009 to 2018 (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2009). The protocol of NHANES (https://www.cdc.gov/nchs/nhanes/about/erb.html) has been approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (NHANES 2005–2010: Protocol #2005-06; NHANES 2011–2018: Protocol #2011-17(Continuation of Protocol #2011-17 Effective through October 26, 2017), Protocol #2018-01 (Effective beginning October 26, 2017). Each participant has provided informed consent prior to the commencement of the survey.

A total of 49,693 participants were enrolled in the study, which aimed to explore the relationship between inflammation indicators and lumbar bone mineral density in depressed individuals who habitually drink alcohol. Dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine were conducted at the NHANES Mobile Examination Center (MEC). The spine scans provide bone measurements for the total spine and vertebrae L1 – L4. Accordingly, participants without depressive symptoms (34056 individuals) and drinking inhibits (1806 individuals) were excluded. Additionally, individuals lacking data about bone mineral density data (2918 participants), monocyte (8805 participants), or high-density lipoprotein cholesterol (53 participants) were also excluded. Following the completion of this screening process, the research encompassed a total of 2,055 alcohol-dependent individuals with depression. The entire process of data selection is shown in Fig. 1.

Depression samples were obtained from participants in the NHANES through the analysis of questionnaire data. The presence of depressive symptoms was determined using the Patient Health Questionnaire-9 (PHQ-9)[13]. The PHQ-9 comprises nine items, as follows: (1) anhedonia, (2) depressed mood, (3) sleep disturbance, (4) fatigue, (5) appetite changes, (6) low self-esteem, (7) concentration problems, (8) psychomotor disturbances, and (9) suicidal ideation. A score of 0–4 is indicative of the absence of depressive symptoms. Conversely, a score of ≥ 5 indicates the presence of depressive symptoms, with varying degrees of severity, and was therefore incorporated into the study cohort[13,14].

Alcohol use questionnaire (ALQ) 130 of NHANES participants was employed to ascertain whether or not an individual engages in the consumption of alcohol. The ALQ130 mainly consisted of the following question: during the past 12 months, on those days that you/SP drank alcoholic beverages, on the average, how many drinks did you/SP have? Based on ALQ130, NHANES respondents were classified into two categories: those who rarely or never drink (i.e., “hardly drinkers”) and those who do drink (i.e., " alcohol-dependent individuals”). Only alcohol-dependent individuals were therefore incorporated into this study.

Systemic inflammation indicators

A complete blood count (CBC) was conducted via a Beckman Coulter analyzer, comprising the measurement of white blood cells (WBCs) and platelets. Concurrently, the WBCs were classified into three respective subtypes, including neutrophils, lymphocytes, and monocytes. Certain composite indicators associated with white blood cells, including MHR, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), serve as reflective measures of the patient’s inflammatory status.

Covariates

Demographic information, including age, gender, race/ethnicity, marital status, educational attainment, and family poverty income ratio (PIR) was collected via self-reported questionnaires. Anthropometric measurements such as lumbar bone mineral density, body mass index (BMI) and waist circumference were obtained using standardized protocols. Blood samples were collected to measure levels of high-density lipoprotein cholesterol

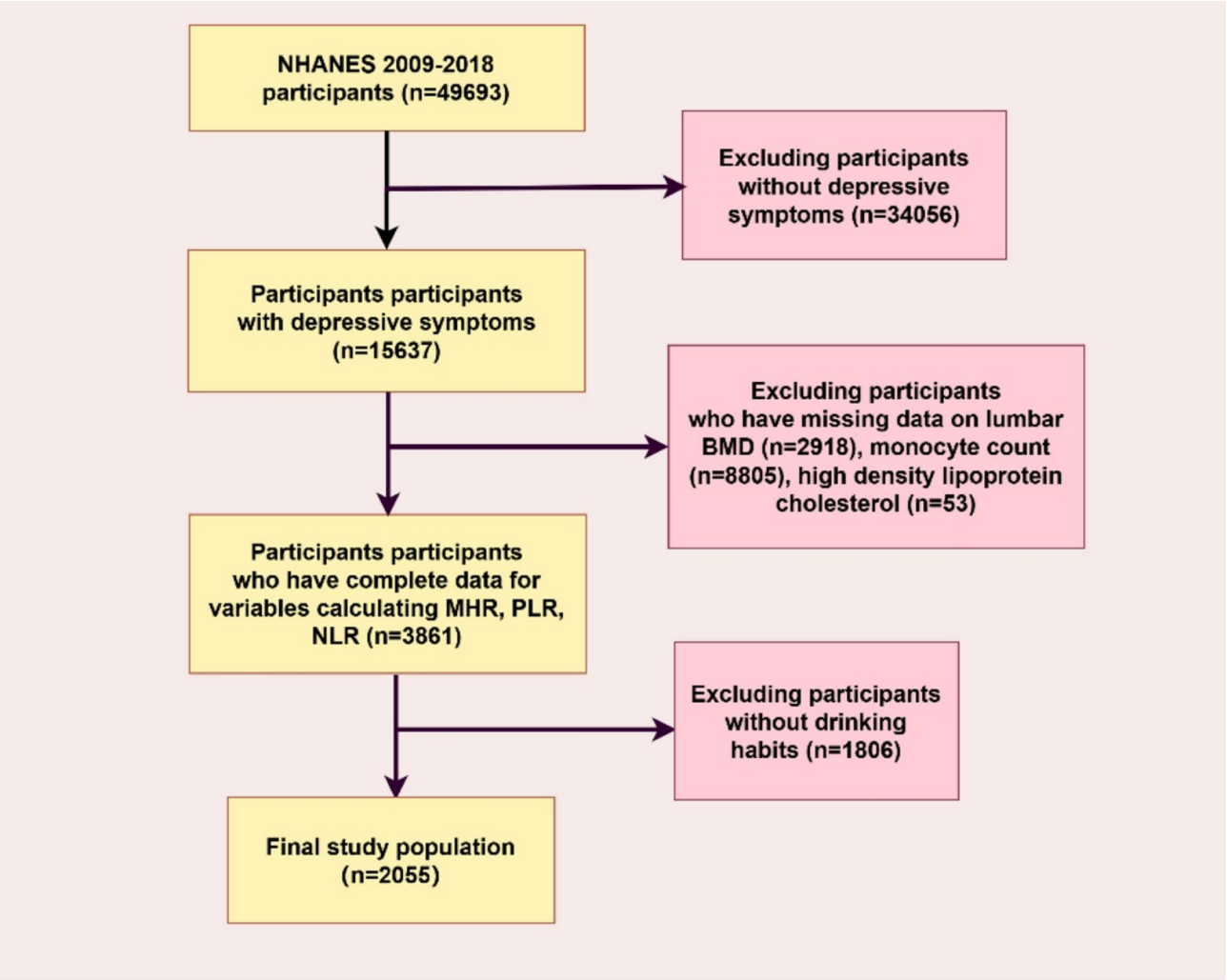

Fig. 1. Flowchart of participants included in the analyses.

(HDL-C), total calcium (Ca), serum iron (Fe), and vitamin D (VitD). Diabetes status, hypertension status, smoking status, and drinking habit were also recorded.

Statistical analysis

Descriptive statistics were utilized to encapsulate the demographic and clinical attributes of the participants. Multivariate regression models were applied to evaluate the association between lumbar BMD and MHR, with adjustments made for potential confounding variables. Subgroup analyses were performed to investigate the potential effect modification by gender, race, and educational attainment. The nonlinear association between lumbar BMD and the MHR was examined through the application of smooth curve fitting and generalized additive models. Upon identifying nonlinearity, a recursive method was employed to ascertain the inflection point in the relationship between lumbar BMD and MHR. Subsequently, a two-piecewise linear regression model was applied to each segment delineated by the inflection point. Statistical analysis was conducted using R (version 4.2.0) in combination with EmpowerStats software, with a P value of 0.05 considered statistically significant.

Results

Baseline characteristics of participants

At baseline, the study enrolled a total of 2055 alcohol-dependent individuals with depression, with a mean age of 37.202 years and a standard deviation of 12.696. The clinical characteristics of the participants according to the lumbar BMD quartiles are shown in Table 1, revealing significant variations in age, gender, race/ethnicity, education, BMI, VitD, and monocyte across the quartiles ($P<0.05$). Alcohol-dependent individuals with depression in the top lumbar BMD quartile were much likely to be female, non-Hispanic white, some college or AA degree, with higher BMI, VitD, and lower monocyte and MHR when compared to the other categories. No statistically significant associations were found between smoking history, family poverty income ratio, marital

Lumbar BMD (g/cm²)	Total	Q 1 0.554–0.930	Q 2 0.930–1.022	Q 3 1.022–1.125	Q 4 1.125–1.754	*P*-value
N (%)	2055 (100.00)	508 (24.72)	517 (25.16)	514 (25.01)	516 (25.11)	
Age (years)	2055 (37.202 ± 12.696)	38.875 ± 12.901	36.947 ± 12.892	35.487 ± 11.333	38.193 ± 12.160	< 0.001
Gender (%)						0.005
Male	1013 (49.294%)	55.951	50.165	47.184	45.716	
Female	1042 (50.706%)	44.049	49.835	52.816	54.284	
Race/ethnicity (%)						< 0.001
Mexican American	342 (16.642%)	13.715	12.007	10.883	6.305	
Other Hispanic	231 (11.241%)	10.584	7.039	7.264	5.850	
Non-Hispanic White	816 (39.708%)	64.043	59.894	61.137	60.669	
Non-Hispanic Black	429 (20.876%)	5.526	11.044	12.386	18.576	
Other Race	237 (11.533%)	6.132	10.015	8.330	8.600	
Education (%)						0.011
Less than 9th grade	121 (6.234%)	3.974	4.335	2.197	3.818	
9–11th grade	329 (16.950%)	15.603	13.460	11.181	11.422	
High school graduate/GED	491 (25.296%)	27.601	23.541	29.003	21.914	
Some college or AA degree	695 (35.806%)	34.476	37.162	35.576	44.337	
College graduate or above	305 (15.714%)	18.347	21.502	22.044	18.508	
Smoking history (%)						0.192
Never	817 (40.506%)	36.917	39.052	40.761	39.862	
Previous	333 (16.510%)	18.312	15.664	20.497	20.001	
Now	867 (42.985%)	44.770	45.284	38.742	40.137	
Family poverty income ratio	1895 (2.028 ± 1.539)	2.413 ± 1.563	2.390 ± 1.678	2.480 ± 1.602	2.510 ± 1.660	0.642
Marital status (%)						0.708
Yes	650 (33.488%)	34.563	33.710	36.615	36.627	
No	1291 (66.512%)	65.437	66.290	63.385	63.373	
Hypertension (%)						0.504
Yes	439 (79.385%)	84.299	80.229	78.022	83.951	
No	114 (20.615%)	15.701	19.771	21.978	16.049	
Diabetes (%)						0.075
Yes	149 (7.409%)	3.990	4.958	7.079	7.112	
No	1862 (92.591%)	96.010	95.042	92.921	92.888	
BMI (kg/m²)	2051 (27.631 ± 6.854)	28.635 ± 6.892	28.852 ± 6.591	29.667 ± 7.816	29.630 ± 7.472	0.039
Waist circumference (cm)	2031 (98.717 ± 17.389)	98.879 ± 16.815	98.079 ± 16.432	98.717 ± 18.739	98.902 ± 17.047	0.863
Total calcium (Ca, mg/dL)	2045 (9.383 ± 0.353)	9.388 ± 0.382	9.402 ± 0.323	9.382 ± 0.339	9.368 ± 0.348	0.494
Serum iron (Fe, ug/dL)	2044 (15.576 ± 7.292)	16.237 ± 7.173	16.414 ± 7.322	15.447 ± 6.533	16.154 ± 8.019	0.163
VitD (nmol/L)	2055 (59.187 ± 24.913)	64.217 ± 25.596	64.553 ± 25.651	61.716 ± 21.114	67.285 ± 28.601	0.006
HDL-C (mg/dL)	2055 (52.258 ± 16.596)	53.429 ± 18.409	52.095 ± 16.126	51.614 ± 16.161	54.031 ± 17.334	0.081
Monocytes (1000 cells/uL)	2055 (0.571 ± 0.201)	0.594 ± 0.214	0.598 ± 0.205	0.573 ± 0.190	0.560 ± 0.184	0.007
Lymphocytes (1000 cells/uL)	2055 (2.297 ± 0.731)	2.230 ± 0.707	2.272 ± 0.794	2.310 ± 0.744	2.247 ± 0.700	0.325
Neutrophils (1000 cells/uL)	2055 (4.478 ± 2.238)	4.438 ± 1.871	4.449 ± 1.726	4.606 ± 2.289	4.478 ± 1.824	0.482
Platelets (1000 cells/uL)	2055 (248.007 ± 62.550)	246.445 ± 60.930	240.797 ± 59.641	247.950 ± 61.553	245.724 ± 59.524	0.270
MHR	2055 (0.012 ± 0.006)	0.012 ± 0.006	0.013 ± 0.006	0.012 ± 0.006	0.012 ± 0.006	0.024
PLR	2055 (117.254 ± 44.251)	120.136 ± 44.534	116.102 ± 44.047	115.493 ± 38.778	118.516 ± 43.683	0.267
NLR	2055 (2.082 ± 1.040)	2.144 ± 1.128	2.134 ± 1.019	2.083 ± 0.868	2.139 ± 0.995	0.754

Table 1. Baseline cohort characteristics. Mean ± SD for continuous variables: the P-value was calculated by the weighted linear regression model. (%) for categorical variables: the P-value was calculated by the weighted chi-square test. *BMD* bone mineral density, *BMI* body mass index, *VitD* vitamin D, *HDL-C* high-density lipoprotein cholesterol, *MHR* monocyte to HDL-C ratio, *PLR* platelet to lymphocyte ratio, *NLR* neutrophil to lymphocyte ratio.

status, hypertension, diabetes, waist circumference, total calcium, serum iron, HDL-C, neutrophils, lymphocytes, platelets, PLR and NLR ($P > 0.05$).

The association between monocyte to HDL-C ratio and lumbar bone mineral density

The results of the multivariate regression analysis are presented in Table 2; Fig. 2. In the unadjusted model, MHR exhibited a negative association with lumbar BMD (β=-1.099, 95% CI: -2.109 to -0.089, $P = 0.033$). This

	MODEL 1 β (95% CI)	MODEL 2 β (95% CI)	MODEL 3β (95% CI)
	P-value	*P*-value	*P*-value
MHR	− 1.099 (− 2.109, − 0.089)	− 1.283 (− 2.408, − 0.158)	− 1.681 (− 3.218, − 0.144)
	0.033	0.026	0.032
Quintiles of MHR			
Q1	Reference	Reference	Reference
Q2	0.001 (− 0.017, 0.018)	− 0.003 (− 0.022, 0.015)	− 0.010 (− 0.031, 0.011)
	0.938	0.712	0.331
Q3	− 0.026 (− 0.044, − 0.008)	− 0.030 (− 0.049, − 0.012)	− 0.039 (− 0.062, − 0.015)
	0.004	0.002	0.001
Q4	− 0.020 (− 0.038, − 0.003)	− 0.025 (− 0.045, − 0.006)	− 0.035 (− 0.062, − 0.008)
	0.024	0.011	0.011
P for trend	0.005	0.003	0.011

Table 2. The association between monocyte to HDL-C ratio and lumbar bone mineral density. Model 1: no covariates were adjusted. Model 2: age, gender, educational level and BMI were adjusted. Model 3: age, gender, educational level, BMI, family income-to-poverty ratio, Total calcium, Serum iron, VitD, HDL-C, lymphocytes, neutrophils, platelets, PLR and NLR were adjusted. *HDL-C* high-density lipoprotein cholesterol, *MHR* monocyte to HDL-C ratio.

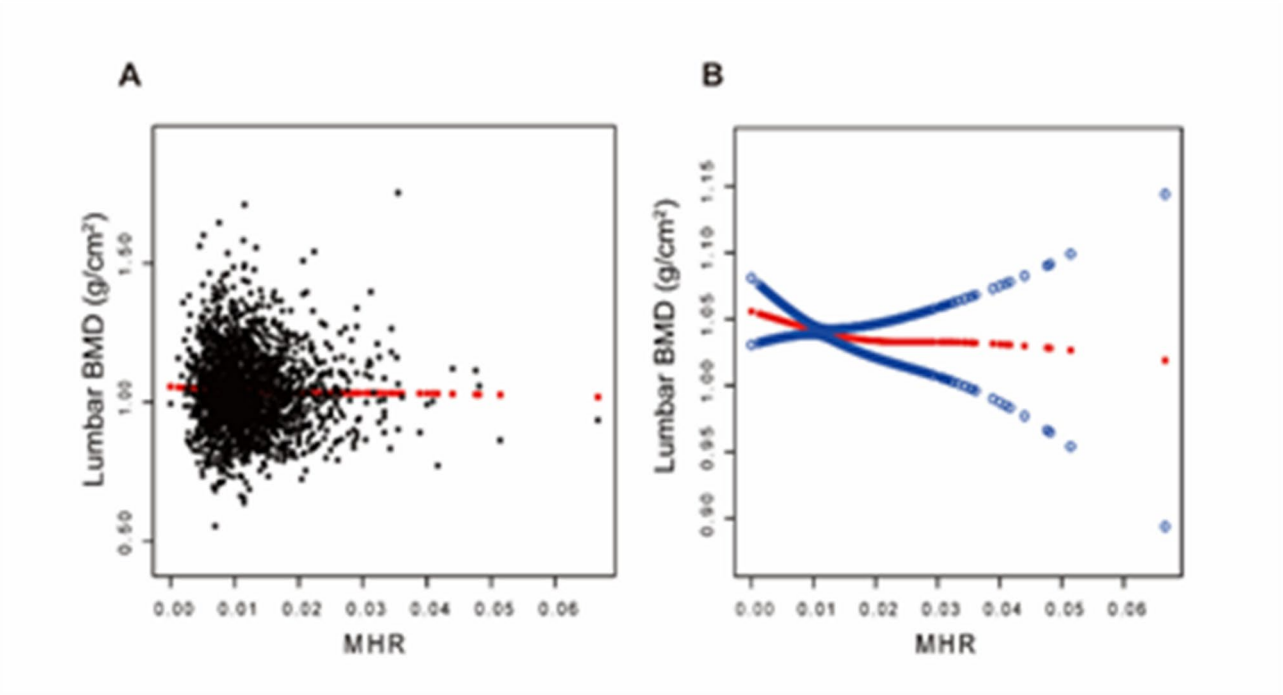

Fig. 2. The association between monocyte to HDL-C ratio and lumbar bone mineral density in alcohol-dependent individuals with depression. (**A**) Each black point represents a sample. (**B**) Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Age, gender, educational level, BMI, family income-to-poverty ratio, Total calcium, Serum iron, VitD, HDL-C, lymphocytes, neutrophils, platelets, PLR and NLR were adjusted. *HDL-C* high-density lipoprotein cholesterol, *MHR* monocyte to HDL-C ratio.

significant relationship persisted after adjusting for covariates in model 2 (β=-1.283, 95% CI: -2.408 to -0.158, $P = 0.026$) and model 3 (β=-1.681, 95% CI: -3.218 to -0.144, $P = 0.032$). Furthermore, when MHR was categorized into quartiles, individuals in the lowest MHR quartile exhibited a 0.02 g/cm² higher lumbar BMD compared to those in the highest MHR quartile ($P < 0.001$ for trend).

Subgroup	Crude β (95% CI)	*P* for interaction	MODEL 1 β (95% CI)	*P* for interaction
Stratified by gender		0.192		0.325
Men	−1.625 (−2.937, −0.313)		−0.942 (−2.513, 0.629)	
Women	−0.190 (−1.905, 1.525)		0.159 (−1.943, 2.262)	
Stratified by race		0.767		0.735
Mexican American	0.934 (−1.283, 3.150)		0.549 (−1.863, 2.961)	
Other Hispanic	−0.085 (−3.107, 2.938)		−0.784 (−4.015, 2.447)	
Non-Hispanic White	−0.473 (−1.956, 1.011)		−0.835 (−2.697, 1.027)	
Non-Hispanic Black	−0.350 (−3.065, 2.366)		−0.830 (−3.920, 2.261)	
Other Race	−1.460 (−4.461, 1.541)		−2.190 (−5.540, 1.159)	
Stratified by education		< 0.001		0.001
Less than 9th grade	8.140 (4.006, 12.274)		7.556 (3.432, 11.679)	
9–11th grade	−1.420 (−3.701, 0.860)		−0.889 (−3.267, 1.490)	
High school graduate/GED	−1.624 (−3.526, 0.277)		−1.695 (−3.784, 0.394)	
Some college or AA degree	−0.966 (−2.755, 0.823)		−0.972 (−3.038, 1.094)	
College graduate or above	−1.912 (−5.322, 1.498)		−2.015 (−5.680, 1.651)	

Table 3. Subgroup analyses of the association of the monocyte to HDL-C ratio with lumbar bone mineral density. Crude: no covariates were adjusted. Model 1: age, gender, race, educational level, BMI, Total calcium, Serum iron, VitD, HDL-C, lymphocytes, neutrophils, platelets, PLR and NLR were adjusted. In the subgroup analysis stratified by gender, race, and educational level, the model is not adjusted for gender, race, and educational level respectively. *HDL-C* high-density lipoprotein cholesterol, *GED* General Educational Development.

	Adjusted β (95% CI) *P*-value
High school graduate/GED	
Inflection point	0.024
MHR < 0.024	1.676 (−11.795, 15.147) 0.808
MHR > 0.024	30.307 (8.152, 52.462) 0.009
Log likelihood ratio	0.031

Table 4. Adjusted associations between monocyte to HDL-C ratio with lumbar bone mineral density by education level. Age, gender, race, BMI, Total calcium, Serum iron, VitD, HDL-C, monocytes, lymphocytes, neutrophils, platelets, hypertension, diabetes, PLR and NLR were adjusted. *HDL-C* high-density lipoprotein cholesterol, *MHR* monocyte to HDL-C ratio.

Subgroup analyses of the association of the monocyte to HDL-C ratio with lumbar bone mineral density after adjustment for confounding factors

Subgroup analyses stratified by gender and educational attainment revealed significant interactions, particularly within the educational subgroups (Table 3). Specifically, when stratified by gender, the negative correlation between MHR and lumbar BMD remained significant in men (β=-1.625, 95% CI: -2.937, -0.313, $P<0.05$). Conversely, no significant differences were observed in the correlation between MHR and BMD across various ethnic groups ($P>0.05$). Notably, individuals with less than a 9th-grade education exhibited a positive association with MHR, whereas those with a college degree or higher demonstrated a negative association ($P<0.001$ for interaction). In the fully adjusted model, this correlation was still significant ($P=0.001$ for interaction).

U-shaped association between MHR and lumbar BMD in individuals possessing a high school diploma or GED equivalent

The stratified analysis examining the association between the monocyte-to-high-density lipoprotein ratio and lumbar bone mineral density, while adjusting for multiple covariates across varying levels of educational attainment, reveals a significant U-shaped relationship in the subgroup of individuals possessing a high school diploma or GED equivalent, as detailed in Table 4; Fig. 3. Notably, within this educational stratum, MHR levels below the threshold of 0.024 are associated with an adjusted β-value of 1.676, with a 95% Confidence Interval (CI) extending from −11.795 to 15.147. This interval includes zero, suggesting the absence of a statistically significant association at this MHR level ($P=0.808$). In contrast, at MHR levels greater than 0.024, the adjusted β-value increases significantly to 30.307, with a 95% confidence interval ranging from 8.152 to 52.462, indicating a strong positive correlation that is statistically significant ($P=0.009$). The log-likelihood ratio test supports the model's goodness-of-fit with a P-value of 0.031, thereby confirming the statistical reliability of the observed U-shaped association.

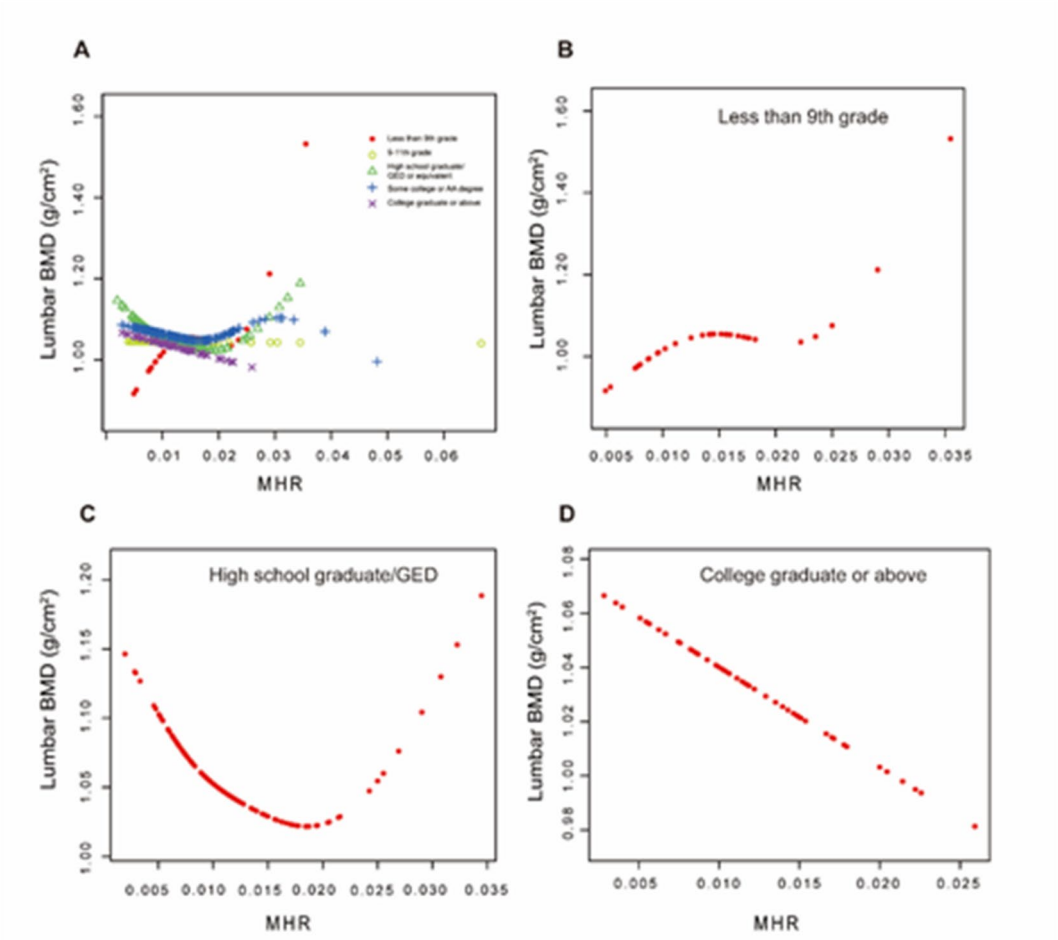

Fig. 3. Multivariable-adjusted associations between monocyte to HDL-C ratio and lumbar bone mineral density in individuals with alcohol-dependency and depression stratified by educational level. (**A**) the whole population; (**B**) less than 9th grade; (**C**) high school graduate/GED; (**D**) college graduate or above. Age, gender, race, BMI, Total calcium, Serum iron, VitD, HDL-C, monocytes, lymphocytes, neutrophils, platelets, hypertension, diabetes, PLR and NLR were adjusted. *BMD* bone mineral density, *GED* General Educational Development, *MHR* monocyte to HDL-C ratio.

The U-shaped relationship indicates a nuanced impact of MHR on health outcomes within this educational stratum, wherein the influence of MHR is minimal at lower levels but becomes significantly positive beyond a certain threshold. This nonlinear association may reflect intricate biological interactions between MHR and lumbar BMD, as well as potential disparities in socioeconomic and behavioral factors. It underscores the necessity for tailored public health interventions that address the specific needs of distinct educational groups.

Discussion

Alcohol dependence and depression

Alcohol misuse is the primary contributor to disease and death in both developed and developing nations. Quantitative data on alcohol misuse underscores its substantial medical significance. When evaluating its contribution to physical ailments and self-inflicted fatalities, alcoholism ranks as the fourth leading cause of death within the United States[15,16]. Depression is frequently identified as the predominant comorbid psychiatric disorder in patients exhibiting alcohol dependence[17,18]. Given the prevalent manifestation of depressive symptoms in individuals with alcoholism, clinicians and researchers hypothesize a potential correlation between these two disorders. It is postulated that individuals may resort to alcohol consumption as a coping mechanism for underlying depressive conditions. Conversely, depression may predominantly arise as a detrimental consequence of alcohol dependence[15]. The primary criterion for evaluation is predicated on the precedence or the fundamental cause. It is evident that the concurrent prevalence of depression and alcohol dependence is not only common but also clinically significant. Focusing solely on either alcoholism or depression presents a skewed perspective. In general, the elevated incidence of alcohol abuse among individuals suffering from depression indicates that research into this demographic and enhancement of their physical and mental well-being could potentially have a substantial influence on public health.

Clinical implications

Osteoporosis, alcohol dependence and depression have become major public health concerns in increasingly aging population, both of them are closely associated with severe morbidity and increased mortality. A previous cross-sectional study published in 2022 indicates that people with depression was associated with lower BMD, particularly in the spine, males, Hispanic-White, and not highly educated populations[19]. This association between depression and lower BMD is stable and consistent with previous research findings[7,20–22]. A research based on trabecular bone score (TBS) rather than BMD showed that alcohol use disorder, antidepressants, and lithium are associated with poorer bone texture in women[23]. Although alcohol dependence and depression often occur simultaneously, previous studies on bone metabolism in alcohol dependent patients with depression were limited and further exploration was needed.

As the main risk factor of osteoporosis, chronic low inflammation caused by depression and alcohol can directly influence bone homeostasis[24–26]. The NLR, PLR and MHR are biomarkers of inflammation and oxidative stress. Especially MHR, is considered as a prognostic biomarker for cardiovascular disease[27,28]. In our cross-sectional study, using NHANES data, we found a significant U-shaped link between MHR and lumbar BMD in high school-educated individuals with alcohol-dependent depression. When the MHR was below 0.024, there was a corresponding increase in lumbar BMD by 1.676 g/cm^2 for each unit increase in MHR. Conversely, when the MHR was precisely 0.024, the BMD was observed to be at its minimal value. However, when the MHR exceeded 0.024, the BMD exhibited a substantial increase of 30.307 g/cm^2 for each unit increment in MHR. These results indicated that MHR may have a threshold effect on bone health, shedding light on the intricate relationship between systemic inflammation, metabolic factors, and bone mineral density.

To our knowledge, only two prior investigations have been conducted on the correlation between MHR and BMD levels. A cross-sectional study executed in 2024 suggests that, among the non-diabetic elderly population, MHR serves as a defensive mechanism against bone irregularities, exhibiting a direct relationship with lumbar BMD[(11)]. In the context of Chinese postmenopausal women diagnosed with Type 2 Diabetes Mellitus (T2DM), both MHR and Monocyte to Albumin Ratio (MAR) demonstrated a positive correlation with beta-C-terminal telopeptide (β-*CTX*), and a negative correlation with lumbar and femoral neck BMD[29]. The correlation between other inflammatory indices derived from blood cell count and BMD exhibits varying results across different demographic groups. A preceding retrospective analysis involving 893 postmenopausal women revealed a negative correlation between BMD and systemic immune-inflammation index (SII), NLR, and the product of platelet count and neutrophil count (PPN). These factors were also found to be positively associated with the risk of osteoporosis[30]. This was further corroborated by a cross-sectional study of 413 postmenopausal women, which also demonstrated a negative relationship between SII and BMD[31]. Additionally, research conducted in Turkey indicated an inverse correlation between BMD and NLR, PLR, MLR, and SII in postmenopausal women[32]. Research investigating children diagnosed with hypothyroidism has revealed a significant positive correlation between the BMD Z-score and NLR, MLR, PLR, and thyroid stimulating hormone (TSH) levels. However, this correlation was not observed in children who were either healthy or diagnosed with hyperthyroidism[33]. A separate retrospective study involving 143 children demonstrated a negative correlation between the BMD Z-score and both MLR and PLR in the obese cohort, while a positive correlation was identified within the control group[34]. Chen et al. discovered no significant correlation between MLR and lumbar BMD in adults. However, they noted a positive correlation between NLR and lumbar BMD, and a negative correlation between PLR and lumbar BMD[35]. This is further supported by a meta-analysis, which also suggested a negative correlation between both NLR and PLR with BMD[36].

To the best of our knowledge, this is the first study monitoring MHR to identify its link to lumbar BMD in alcohol-dependent, depressed patients. The study fills a significant gap in existing literature on the impact of systemic inflammatory markers on BMD patients with alcohol dependence and depression, offering several clinical benefits for doctors. Our research elucidates the interaction between systemic inflammation and bone health within a specific demographic, thereby fostering a comprehensive understanding of the multifactorial determinants of bone density. The implications of these findings could potentially facilitate early identification of individuals at risk and aid in the development of targeted interventions designed to mitigate bone loss and prevent osteoporosis. Moreover, our research has the potential to guide the development of individualized treatment approaches, taking into account the intricate interconnections among alcohol dependence, depressive manifestations, and bone health. This could potentially augment clinical results and ameliorate the life quality of impacted individuals. Additionally, the knowledge derived from this study could provide critical information for public health policymakers, directing the formulation of health management policies specifically designed to cater to the requirements of patients suffering from these coexisting conditions. The study promotes interdisciplinary collaboration in psychiatry, osteology, and immunology, advancing cross-disciplinary research. It provides theoretical and practical contributions to patient care and scientific knowledge in health research.

Strengths and limitations

To date, scholarly investigations concerning BMD have predominantly concentrated on postmenopausal women. The BMD level of patients suffering from alcohol-dependent depression, a subject that has been sparingly addressed in existing literature, remains largely unexplored. This research represents the inaugural study into the association between the systemic inflammatory index and BMD within this particular demographic. This study has a number of strengths, including the use of a combined five cycles of NHANES data based on a nationally representative sample. This benefits from a robust, standardised methodology and a large, nationally representative sample, enhancing the generalisability of the findings. The study's interdisciplinary approach, which brings together psychiatry, bone health and inflammation, makes a significant contribution to our understanding of the complex interactions between mental health and physical well-being.

As a cross-sectional study, this research is limited in its ability to establish causality or temporality between systemic inflammation, alcohol dependence, depression, and bone density. The findings are specific to patients suffering from alcohol-dependent depression and may not be generalizable to other populations with different characteristics or healthcare systems. Reliance on self-reported data for certain variables, such as alcohol consumption and depression symptoms, could introduce reporting biases, affecting the accuracy of the results. Current evidence is mostly limited to studies that used BMD, which does not provide more information about the texture of bone tissue and can underestimate fracture risk[23,37]. The U-shaped link between MHR and BMD in the "High School Graduate/GED" group lacks clear biological explanation. More research is needed to understand why inflammation differently affects the balance between bone formation and resorption.

Conclusion

In conclusion, this study provides novel insights into the relationship between MHR, a marker of systemic inflammation, and BMD in individuals with alcohol dependency and depression. The observed U-shaped association among participants with a high school diploma or GED equivalent highlights the complex interplay between inflammation, metabolic factors, and bone health. Although constrained by its cross-sectional design, this research identifies MHR as a potential biomarker for monitoring bone health in alcohol-dependent individuals with depression. It is recommended that clinicians consider regular BMD assessments and interventions aimed at modulating inflammation in this population. Future studies should seek to confirm these findings in longitudinal cohorts and investigate the underlying mechanistic pathways.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/.

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Author contributions
LZ and XY wrote the main manuscript text, LZ prepared Tables 1, 2, 3 and 4, XY prepared Figs. 1, 2 and 3. All authors contributed to review and approved the submitted version.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
All human subjects involved in this study were treated in accordance with the ethical principles outlined in the Declaration of Helsinki, and the study was approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS). The patients/participants provided their written informed consent to participate in this study.

Additional information
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