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Association between atherogenic coefficient and depression in US adults: a cross-sectional study with data from National Health and Nutrition Examination Survey 2005-2018

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4 **Association between atherogenic coefficient and depression in US**
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6 **adults: a cross-sectional study with data from National Health and**
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8 **Nutrition Examination Survey 2005-2018**
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ABSTRACT

Objective: There are strong comorbidities between depression and cardiovascular disease.

The atherogenic coefficient (AC) is an important index that is linked to cardiovascular disease and has been suggested to play a role in depression. Therefore, we investigated the association between AC and depression among adult Americans.

Design: Cross-sectional study.

Setting: The National Health and Nutrition Examination Survey (2005-2018).

Participants: A total of 32502 participants aged 20 years or older who had complete information for AC and depression were included in this study.

Primary and secondary outcome measures: Whether the patient suffered from depression. AC values were calculated from cholesterol and high-density lipoproteins. Covariates including age, sex, race/ethnicity, body mass index, poverty-income ratio, educational level, marital status, hypertension, diabetes mellitus, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin level were adjusted in multivariate logistic regression models.

Results: After adjusting for potential confounders, a single unit increase in AC was associated with a 4% increase in the prevalence of depression (hazard ratio =1.04, 95% confidence interval =1.02-1.07, $P = 0.002$). The relationship between AC and depression was more obvious in females.

Conclusions: The AC is positively associated with depression.

Keywords: atherosclerosis, depression, nutrition surveys, adult

Strengths and Limitations: 1. The quality and scale of the National Health and Nutrition Examination Survey database and the rigour of its measures ensure the statistical power and reliability of our results. 2. A wide range of sociodemographic, lifestyle and physical health covariates were adjusted for, reducing the possibility of residual confounding. 3. This study was limited by its cross-sectional design, and no causal relationships could be determined. 4. The PHQ-9 is a proven, simple, and effective tool for identifying the severity of depressive symptoms, but it is not a diagnostic tool for Major Depressive Disorder (MDD).

INTRODUCTION

Depression is a clinically common emotional state characterized by a persistent feeling of sadness or inability to experience pleasure, accompanied by deficits in daily functioning [1]. In 2008, the World Health Organization (WHO) ranked major depression as the third leading cause of the global burden of disease and projected that it would be the number one cause by 2030 [2]. More than 300 million people worldwide suffer from major depressive disorder (MDD) [3], and this number has increased over the past decade [4]. Depression can cause various adverse events, seriously endangering lives and global health [5,6]. Current antidepressant treatments are effective, but there are many side effects; for example, antidepressants may increase suicidal thoughts in some people [7]. Evidence supports screening for depression and providing early intervention [8]. Therefore, it is necessary to explore the factors related to depression. Abnormal lipid metabolism is often observed in patients with depression. Some studies have shown that changes in circulating lipid concentrations may be associated with depression [9]. Lipids play a role in depression via inflammation and metabolic changes. On one hand, activation of the proinflammatory response leads to a decrease in high-density lipoprotein (HDL) and phospholipids and a compensatory increase in phospholipid-rich low-density lipoprotein (LDL), which in turn slows total cholesterol (TC) metabolism and affects neurotransmitters and neural circuits that contribute to behavioral symptoms of depression [10]. On the other hand, cytokine signaling in adipose tissue, particularly tumor necrosis factor (TNF), promotes metabolic dysregulation and increases depression [11].

The pathogenesis of atherosclerosis is based on the lipid theory, and the explanation is related to excess cholesterol being the sole cause of lipid deposition in the arterial wall [12]. The atherogenic coefficient (AC) is an important index for assessing the degree of atherosclerosis, which is calculated as $(TC - HDL)/HDL$ [13]. Nunes et al. found that AC was elevated in patients with MDD and bipolar disorder and was also associated with cardiovascular disease (CVD) [14]. AC and CVD can be controlled by statins and other cardiovascular drugs [15,16]. Exploring the role of AC

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4 in depression may be beneficial for the treatment of depression and depression
5 combined with CVD.
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7 To the best of our knowledge, the role that AC plays in depression is still
8 unclear. Therefore, we used data from the National Health and Nutrition Examination
9 Survey (NHANES) database to explore the association of AC with depression in
10 adults.
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15 16 17 **METHODS**

18 19 **Study design and participants**

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21 Data of the participants in this study were obtained from the NHANES database, a
22 major program conducted by the Centers for Disease Control and Prevention (CDC)
23 to assess the health and nutritional status of 5,000 adults and children in the US
24 annually [17]. The NHANES database contains demographic, dietary, examination,
25 laboratory, and questionnaire data. The National Center for Health Statistics (NCHS)
26 Research Ethics Review Board (ERB) authorized the NHANES study protocols.
27 Further information regarding the NHANES data can be obtained from its official
28 website (<http://www.cdc.gov/nchs/nhanes.htm>).
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37 Participants in our study were screened according to the following inclusion
38 criteria: 1) aged 20 years or above, and 2) participation in laboratory tests on an empty
39 stomach. The exclusion criteria were as follows: 1) incomplete Patient Health
40 Questionnaire-9 (PHQ-9) and 2) no data on total cholesterol or high-density
41 lipoprotein levels.
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46 47 **Assessment of depression**

48 The PHQ-9 is used to assess depression. The PHQ-9 contains nine items that capture
49 the frequency of depressive symptoms such as: appetite problems, fatigue, sleep
50 difficulties, psychomotor retardation or agitation, concentration problems, lack of
51 interest, depressed mood, feelings of worthlessness, and suicidal ideation. It is now
52 widely accepted as an accurate and reliable method for screening depression [18,19].
53 Each question is scored from '0' (not at all) to '3' (nearly every day), with a total
54 score of 0–27 where a score ≥ 10 is considered clinically relevant depression (CRD)
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4 [20]. PHQ-9 sensitivity compared with semi-structured diagnostic interviews was
5 greater than that in previous conventional meta-analyses that combined reference
6 standards. A cutoff score of 10 or above maximized the combined sensitivity and
7 specificity overall and for subgroups [21].
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11 **Assessment of AC**

12 Fasting blood was drawn from individuals aged ≥ 20 years, and the blood samples
13 were processed, stored, and shipped to the Johns Hopkins University Lipoprotein
14 Assay Laboratory at the Ambulator-Testing Center laboratory. HDL levels were
15 measured directly in the serum. The apolipoprotein B (apoB)-containing lipoproteins
16 in the specimen were reacted with a blocking reagent that rendered them non-reactive
17 with the enzymatic cholesterol reagent under the assay conditions. Reagents were
18 purchased from Roche/Boehringer-Mannheim Diagnostics (Mannheim, Germany).
19 The method uses sulfated alpha-cyclodextrin in the presence of Mg^{+2} , which forms
20 complexes with apoB-containing lipoproteins, and polyethylene glycol-coupled
21 cholesteryl esterase and cholesterol oxidase for HDL cholesterol measurement. HDL
22 cholesterol data collected from participants in 2005-2006 were adjusted using the
23 following equation: corrected HDL = (Solomon Park assigned HDL value) \times
24 (participant HDL). Total cholesterol was measured enzymatically in the serum or
25 plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize
26 the 3-OH group of cholesterol. All the information can be obtained from
27 <https://wwwn.cdc.gov/Nchs/Nhanes/>.
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44 **Assessment of covariates**

45 Covariates in this study, including body mass index (BMI), alcohol intake, physical
46 activity, and glycosylated hemoglobin, were used as continuous variables. BMI was
47 measured as weight (kg) divided by height (m) squared (<25.0 kg/m² indicating
48 normal, 25.0 to <30.0 kg/m² indicating overweight, ≥ 30.0 kg/m² indicating obese).
49 Alcohol intake (the mean alcohol intake from the first and second dietary surveys was
50 extracted, in which alcohol intake was defined as the alcohol intake on a single day
51 for participants who consumed alcohol on a total of one day ever). Physical activity
52 was self-reported by participants as either inactive, moderate, or vigorous. Categorical
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4 variables included age (20–40 years, 40–60 years, ≥ 60 years), sex (male or female),
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6 and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American,
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8 other Hispanic, or other race/multiple races). The poverty-income ratio (PIR) was
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10 defined as the ratio of family income to poverty threshold (< 1 indicating an income
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12 below the poverty threshold and ≥ 1 indicating an income above the poverty threshold;
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14 the latter category was further divided into two groups: 1.00 to < 2.00 and ≥ 2.00).
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16 Education level was categorized as high school not completed, high school
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18 completed, or high school graduate and some college or associated degrees pursued.
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20 Marital status was defined as married/living with partner or
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22 widowed/divorced/separated/never married. Hypertension (HTN) (defined as systolic
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24 blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) was determined
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26 using three blood pressure measurements at different times, an existing diagnosis, or
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28 evidence of an existing antihypertensive medication regimen. Diabetes mellitus (DM)
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30 was defined as either taking glucose-lowering therapies, a glycated hemoglobin
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32 (HbA1c) concentration of $\geq 6.5\%$, use of anti-diabetic medication, oral glucose
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34 tolerance test (OGTT) ≥ 11.1 mmol/L, fasting plasma glucose ≥ 7.0 mmol/L, or
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36 random blood glucose ≥ 11.1 mmol/L. Smoking status was defined as people who do
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38 not smoke, < 100 cigarettes during lifetime; people who formerly smoked, not
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40 currently smoking but ≥ 100 cigarettes consumed previously; and people who smoke
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42 ≥ 100 cigarettes every day or some days.

43 **Statistical analysis**

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45 The main concern was whether AC is associated with depression after adjusting for
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47 other factors that may influence depression. Continuous variables are expressed as
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49 mean \pm standard deviation, and categorical variables are expressed as percentages.
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51 The χ^2 test was used to compare categorical variables between groups, one-way
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53 analysis of variance was used to compare normally distributed variables between
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55 groups, and Kruskal-Wallis H test was used to compare variables with a skewed
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57 distribution between groups. Multivariate logistic regression analysis was performed
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59 to evaluate the independent association between AC and depression. The participants
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were divided into four groups based on AC: < 1.9310 , 1.9310 to < 2.6695 , 2.6695 to $<$

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4 3.6430, and ≥ 3.6430 . We used three levels of adjustment: Model 1 was adjusted for
5 age, sex, and race/ethnicity; Model 2 was adjusted for the variables in Model 1 plus
6 BMI, PIR, educational level, and marital status; and Model 3 was adjusted for the
7 variables in Model 2 plus HTN, DM, alcohol intake, smoking status, physical activity,
8 and glycosylated hemoglobin. The imputation of missing data was conducted using
9 the missForest R package, which is a random forest-based technique that is highly
10 computationally efficient for high-dimensional data consisting of both categorical and
11 continuous predictors; the missing values are presented in the table (Table S1) [22].
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19 All analyses were performed using R software (The R Foundation, Vienna,
20 Austria) and Empower (X&Y Solutions, Boston, MA, USA). Statistical significance
21 was defined as a two-sided *P*-value <0.05 .
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27 RESULTS

28 Participant characteristics

29 In this study, 32,502 participants were included (Figure 1). Table 1 shows the
30 characteristics of the participants according to their AC. There were statistically
31 significant differences in age, sex, educational level, race/ethnicity, marital status,
32 PIR, alcohol intake, smoking status, physical activity, BMI, HTN, DM, HbA1c,
33 cholesterol, and HDL between the different AC groups ($P < 0.05$).
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40 Participants with the lowest AC in Q1 (< 1.9310) were likely to be female,
41 younger, more educated, married or cohabitating, wealthier, less physically active,
42 smoked less, consumed more alcohol, had no DM or HTN, and lower HbA1c levels.
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46 By contrast, participants with the highest AC in Q4 (> 3.6430) were likely to
47 be male, > 40 years old, more highly educated, non-Hispanic White, married or
48 cohabitating, wealthier, consumed less alcohol, never smoked, inactive and obese, had
49 HTN, and higher HbA1c and cholesterol levels.
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Table 1. Characteristics of the study population, using National Health and Nutrition Examination Survey data from 2005–2018 (N = 32,502).

Characteristic	Overall	Atherogenic coefficient quartiles†				p-value
		Q1 (< 1.9310)	Q2 (1.9310 to < 2.6695)	Q3 (2.6695 to < 3.6430)	Q4 (≥ 3.6430)	
Sample size, <i>n</i> (%)	32,502 (100)	8,126 (25.00)	8,124 (24.99)	8,125 (25.00)	8,127 (25.00)	
Male, <i>n</i> (%)	15,954 (49.09)	2,882 (35.47)	3,496 (43.03)	4,322 (53.19)	5,254 (64.65)	<0.001
Age, <i>y</i> , <i>n</i> (%)						<0.001
20 to < 40	10,857 (33.40)	3,062 (37.68)	2,753 (33.89)	2,517 (30.98)	2,525 (31.07)	
40 to < 60	10,632 (32.71)	2,089 (25.71)	2,423 (29.83)	2,856 (35.15)	3,264 (40.16)	
≥ 60	11,013 (33.88)	2,975 (36.61)	2,948 (36.29)	2,752 (33.87)	2,338 (28.77)	
Educational level, <i>n</i> (%)						<0.001
$<$ High school	7,841 (24.14)	1,625 (20.01)	1,816 (22.36)	2,055 (25.30)	2,345 (28.89)	
Completed high school	7,486 (23.05)	1,724 (21.23)	1,838 (22.64)	1,965 (24.19)	1,959 (24.14)	
$>$ High school	17,152 (52.81)	4,770 (58.75)	4,466 (55.00)	4,104 (50.52)	3,812 (46.97)	
Race/ethnicity, <i>n</i> (%)						<0.001
Non-Hispanic White	14,112 (43.42)	3,516 (43.27)	3,536 (43.53)	3,461 (42.60)	3,599 (44.28)	
Non-Hispanic Black	6,713 (20.65)	2,212 (27.22)	1,803 (22.19)	1,550 (19.08)	1,148 (14.13)	
Mexican American	5,174 (15.92)	925 (11.38)	1,159 (14.27)	1,466 (18.04)	1,624 (19.98)	
Other Hispanic	3,109 (9.57)	583 (7.17)	752 (9.26)	843 (10.38)	931 (11.46)	
Other race/multiple races	3,394 (10.44)	890 (10.95)	874 (10.76)	805 (9.91)	825 (10.15)	

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4	Marital status, <i>n</i> (%)						<0.001
5							
6	Married/Living with partner	19,532 (60.12)	4,363 (53.71)	4,782 (58.89)	5,067 (62.42)	5,320 (65.48)	
7							
8							
9	Widowed/Divorced/Separated/						
10		12,954 (39.88)	3,761 (46.29)	3,338 (41.11)	3,051 (37.58)	2,804 (34.52)	
11	Never married						
12							
13							
14	PIR, <i>n</i> (%)						<0.001
15							
16	< 1.00	6,103 (20.46)	1,425 (19.08)	1,484 (19.90)	1,478 (19.90)	1,716 (22.97)	
17							
18	1.00 to <2.00	8,001 (26.83)	1,857 (24.86)	1,920 (25.74)	2,075 (27.94)	2,149 (28.76)	
19							
20	≥2.00	15,722 (52.71)	4,188 (56.06)	4,055 (54.36)	3,873 (52.15)	3,606 (48.27)	
21							
22							
23							
24	Alcohol intake, <i>g/day</i> , mean						
25							
26		7.80 (19.98)	10.29 (23.26)	7.50 (19.02)	6.59 (17.43)	6.88 (19.61)	<0.001
27	(SD)						
28							
29							
30	Smoking status, <i>n</i> (%)						<0.001
31							
32	Never smoked	17,828 (54.88)	4,751 (58.50)	4,626 (56.89)	4,470 (55.03)	3,981 (49.02)	
33							
34	Former smoker	7,993 (24.61)	1,888 (23.25)	2,003 (24.67)	2,099 (25.84)	2,003 (24.66)	
35							
36	Current smoker	6,664 (20.51)	1,483 (18.26)	1,489 (18.34)	1,554 (19.13)	2,138 (26.32)	
37							
38							
39							
40	Physical activity, <i>n</i> (%)						<0.001
41							
42	Inactive	14,825 (25.20)	3,302 (46.44)	3,597 (51.02)	3,850 (54.11)	4,076 (57.22)	
43							
44	Moderate	7,339 (25.84)	1,846 (25.96)	1,855 (26.31)	131 (26.44)	1,757 (24.66)	
45							
46	Vigorous	2,094 (7.37)	6,01 (8.45)	534 (7.57)	487 (6.84)	472 (6.63)	
47							
48	Both moderate and vigorous	4142 (14.58)	1362 (19.15)	1064 (15.09)	897 (12.61)	819 (11.50)	
49							
50							
51	BMI, kg/m ² , mean (SD)	29.29 (6.96)	26.59 (6.56)	28.99 (7.12)	30.36 (6.88)	31.20 (6.37)	<0.001
52							
53							
54	HTN, <i>n</i> (%)	13,940 (42.89)	3,211 (39.52)	3,414 (42.02)	3,586 (44.14)	3,729 (45.88)	<0.001
55							
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57							
58	DM, <i>n</i> (%)	6,152 (19.28)	1,322 (16.72)	1,411 (17.79)	1,597 (19.97)	1,822 (22.56)	<0.001
59							
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HbA1c, %, mean (SD)	5.76 (1.08)	5.57 (0.86)	5.68 (0.94)	5.79 (1.06)	5.99 (1.36)	<0.001
Cholesterol, mmol/L, mean (SD)	5.00 (1.09)	4.41 (0.91)	4.76 (0.91)	5.08 (0.92)	5.76 (1.12)	<0.001
HDL cholesterol, mmol/L, mean (SD)	1.37 (0.42)	1.80 (0.43)	1.45 (0.29)	1.24 (0.23)	1.01 (0.21)	<0.001
Depression, <i>n</i> (%)	2871 (8.83)	620 (7.63)	649 (7.99)	762 (9.38)	840 (10.34)	<0.001

Abbreviations: DM, diabetes mellitus; BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HTN, hypertension; PIR, poverty-income ratio (ratio of family income to poverty threshold); SD, standard deviation.

Association between AC and depression

In the fully adjusted model, we observed a linear relationship between AC and depression (Figure 2). The results of the multivariate logistic regression analysis are presented in Table 2. AC was positively correlated with depression in the crude model (odds ratio [OR]= 1.09, 95% confidence interval [CI]:1.07-1.12, $P < 0.0001$). After adjusting for confounders, a significant association between AC and depression was detected in Models 1-3. In Model 3, all variables were adjusted; for every 1 unit increase in AC, the incidence of depression increased by 4% (OR = 1.04, 95% CI = 1.02–1.07, $P = 0.002$).

Table 2. Associations of the atherogenic coefficient with depression (n = 32,502).

	Crude Modela		Model 1b		Model 2c		Model 3d	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Per 1 increase	1.09 (1.07,1.12)	<0.001	1.13 (1.10,1.16)	<0.001	1.08 (1.05,1.11)	<0.001	1.04 (1.02,1.07)	0.002
Quartiles								
Q1 (AC: < 1.9310)	McCarron et al. (2021)		McCarron et al. (2021)		McCarron et al. (2021)		McCarron et al. (2021)	
Q2 (AC: 1.9310 to < 2.6695)	1.05 (0.94,1.18)	0.394	1.09 (0.97,1.22)	0.148	1.00 (0.89,1.12)	0.958	0.99 (0.88,1.11)	0.836
Q3 (AC: 2.6695 to < 3.6430)	1.25 (1.12,1.40)	<0.001	1.37 (1.22,1.53)	<0.001	1.18 (1.05,1.32)	0.006	1.13 (1.01,1.28)	0.040
Q4 (AC: ≥ 3.6430)	1.40 (1.25,1.56)	<0.001	1.63 (1.46,1.83)	<0.001	1.30 (1.15,1.46)	<0.001	1.15 (1.02,1.30)	0.026
<i>p</i> for trend	<0.0001		<0.0001		<0.0001		0.0063	

Abbreviations: AC, atherogenic coefficient.

aModel 1: Adjusted for age, sex, and race/ethnicity.

bModel 2: Adjusted for the variables in Model 1 plus body mass index, poverty-income ratio, educational level, and marital status.

cModel 3: Adjusted for the variables in Model 2 plus hypertension, diabetes mellitus, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin.

After adjusting for age, sex, race/ethnicity, BMI, PIR, educational level, marital status, HTN, DM, alcohol intake, smoking status, and physical activity, compared with participants in the first quartile (AC < 1.9310), the second group (1.9310 to < 2.6695, OR = 0.99, 95% CI = 0.88– 1.11, *P* = 0.836), the third group (2.6695 to < 3.6430, OR = 1.13, 95% CI = 1.01– 1.28, *P* = 0.040), and the fourth

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4 group (≥ 3.6430 , OR = 1.15, 95% CI = 1.02– 1.30, $P = 0.026$) had an increased
5 prevalence of depression (P for trend was significant in all the models).
6

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8 Furthermore, regarding the interaction between sex and the relationship
9 between AC and depression, the relationship was more significant in females (OR =
10 1.07, 95% CI = 1.03–1.11, P for interaction = 0.036).
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14 15 **DISCUSSION**

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17 This cross-sectional study showed an association between AC and depression in
18 adults in the United States. After adjusting for covariates, a positive linear relationship
19 was found between AC and depression.
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23 The details of the mechanism explaining the relationship between AC and
24 depression need to be further explored, and there may be several possible
25 explanations. Lipids and the immune system interact with one another and have a
26 regulatory effect on each other. Dysregulated inflammation promotes susceptibility to
27 depression [23]. Studies have shown that inflammatory cytokines produced in the
28 periphery enter the cells of the central nervous system and can affect
29 neurotransmitters and neural circuits, producing the behavioral symptoms of
30 depression [24]. When T lymphocytes are activated, they not only participate in
31 immune inflammation but also directly contribute to the development of depression
32 when functionally impaired [25,26] Lipid peroxidation and oxidation-specific
33 epitopes are formed, and the levels of antioxidants such as glutathione, glutathione
34 peroxidase, and coenzyme Q10 are reduced, resulting in or aggravating oxidative
35 stress [27,28].
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48 When lipids are abnormal, the inflammatory and oxidative and nitrosative
49 (IO&NS) pathway is further activated [29]. At this time, the increase in binding
50 globin and high-sensitivity C-reactive protein (CRP) is accompanied by a significant
51 increase in interleukin-6 (IL-6), tumor necrosis factor- α , interferon- γ , other
52 pro-inflammatory cytokines, and immune inflammation [30]. These factors lead to
53 defects in serotonin and melatonin through the kynurenine pathway, which is often
54 considered to be one of the main causes of depression [31]. Activation of the IO&NS
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4 pathway leads to mitochondrial dysfunction and subsequent cellular dysfunction [32].
5
6 Previous studies have linked mitochondrial dysfunction in various brain regions to
7
8 depression [33].

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10 Statins have also been shown to have antidepressant effects when
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12 co-prescribed with antidepressants [34]. Lowering the AC index of patients with
13
14 mood disorders improves CVD outcomes [35]. CVD is a heart and blood vessel
15
16 disease characterized by myocardial infarction, angina pectoris, heart failure, heart
17
18 attack and stroke [36]. Etiological studies have shown that the presence of depression
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20 doubles the risk of developing CVD [37]. Factors that contribute towards the link
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22 between depression and cardiac outcome may include alterations in the autonomic
23
24 nervous system, platelet receptors and function, coagulopathic factors,
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26 proinflammatory cytokines, endothelial function, neurohormonal factors, and genetic
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28 linkages [38] At the same time, patient compliance with antidepressant treatment is
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30 relatively poor [39]. Atherosclerosis is a chronic vascular inflammatory disease that is
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32 associated with oxidative stress and endothelial dysfunction [40]. Atherosclerosis is
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34 the underlying cause of CVD and AC is a major indicator of atherosclerosis [41]. Our
35
36 results suggest that AC may play a role in depression. AC may be an indicator of the
37
38 relationship between CVD and depression, and a potential target and marker for the
39
40 treatment of depression or depression combined with CVD. The relevant mechanisms
41
42 remain to be explored further.

43
44 Our study found increased odds of depression with increased AC in adults.
45
46 This suggests that controlling AC may be beneficial for depression prevention. Sex
47
48 may affect this relationship. In the subgroup analysis (Table 3), we found a stronger
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50 relationship between AC and depression in females. The synergistic effect of estrogen
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52 on cognitive and emotional functions may underlie the association between ovarian
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54 hormone fluctuations and depression in females [42]. The induction of indoleamine 2,
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56 3-dioxygenase and deleterious effects of tryptophan catabolizing metabolites
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58 (TRYCATs) play a role in the pathophysiology of depression. Activation of IDO
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60 decreases plasma tryptophan levels and increases TRYCAT synthesis in depressed
individuals. Compared to males, females showed more IDO activation and TRYCAT

production after immune challenge [43]. This sex difference in immune dysregulation may therefore contribute to higher levels of anxiety and depression experienced by females.

Table 3. Subgroup analysis of the effect of the atherogenic coefficient on depression (n = 32502)

Subgroup	Number of participants	OR (95% CI)	P for interaction
Sex, n (%)			0.036
Male	15954	1.01 (0.98, 1.05)	
Female	16548	1.07 (1.03, 1.11)	
Age, n (%)			0.463
20 – < 40	10857	1.06 (1.01, 1.10)	
40 – < 60	10632	1.02 (0.98, 1.06)	
≥ 60	11013	1.06 (1.00, 1.11)	
Educational level, n (%)			0.437
< High school	7841	1.03 (0.99, 1.08)	
Completed high school	7486	1.03 (0.97, 1.08)	
> High school	17152	1.06 (1.02, 1.11)	
Race/ethnicity, n (%)			0.084
Non-Hispanic White	14112	1.06 (1.02, 1.10)	
Non-Hispanic Black	6713	1.00 (0.94, 1.07)	
Mexican American	5174	0.97 (0.91, 1.04)	
Other Hispanic	3109	1.10 (1.03, 1.17)	
Other race/multiple races	3394	1.05 (0.96, 1.15)	
Marital status, n (%)			0.873
Married/living with partner	19532	1.04 (1.01, 1.08)	
Widowed/divorced/separated/never married	12954	1.04 (1.00, 1.08)	
PIR, n (%)			0.854
< 1.00	6103	1.04 (1.00, 1.09)	
1.00 – <2.00	8001	1.04 (1.00, 1.09)	

	≥2.00	15722	1.03 (0.97, 1.08)	
	Smoking status, n (%)			0.100
	Never smoked	17828	1.08 (1.04, 1.13)	
	Formerly smoked	7993	1.03 (0.98, 1.08)	
	Smoke every day/ some days	6664	1.02 (0.97, 1.06)	
	BMI, kg/m ² , mean (SD)			0.478
	Low	10729	1.07 (1.01, 1.14)	
	Middle	10733	1.03 (0.98, 1.07)	
	High	10743	1.04 (1.00, 1.08)	
	Hypertension, n (%)			0.628
	Yes	13940	1.05 (1.01, 1.09)	
	No	18562	1.03 (1.00, 1.08)	
	DM, n (%)			0.886
	Yes	6152	1.04 (0.99, 1.09)	
	No	25761	1.04 (1.01, 1.08)	
	HbA1c, %, mean (SD)			0.827
	Low	8737	1.06 (1.00, 1.12)	
	Middle	10992	1.05 (1.01, 1.10)	
	High	12715	1.04 (1.00, 1.08)	
	CVD, n (%)			0.359
	Yes	3571	1.08 (1.01, 1.14)	
	No	28927	1.04 (1.01, 1.08)	

Abbreviations: AC, atherogenic coefficient; BMI, body mass index (calculated as weight, in kilograms, divided by the square of height, in meters); CVD, cardiovascular disease; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; HTN, hypertension; PIR, poverty-income ratio (ratio of family income to poverty threshold).

This study has some limitations. First, this was a cross-sectional study; therefore, we could not determine a causal relationship between AC and depression. Second, the PHQ-9 is a proven, simple, and effective tool for identifying the severity of depressive symptoms, but it is not a diagnostic tool for MDD.

CONCLUSIONS

Our research shows that in American adults, a higher AC is positively related to a higher prevalence of depression. Further studies are required to explore the underlying mechanisms and potential benefits of controlling AC levels in patients with depression.

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Data Sharing Statement: The datasets generated and/or analyzed during the current study are available in the NHANES repository [<https://www.cdc.gov/nchs/nhanes/>].

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19 **FIGURE LEGENDS**

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21 **Figure 1.** Flowchart for inclusion of study participants.

22
23 **Figure 2.** Association between AC and depression in US adults (n=4759). The black
24 vertical line on the horizontal axis represents the caffeine distribution, the red line
25 represents the best fit, and the difference between the dashed lines represents the 95%
26 confidence interval. The data was adjusted for age, sex, race/ethnicity, body mass
27 index, poverty-income ratio, educational level, marital status, hypertension, diabetes
28 mellitus, alcohol intake, smoking status, physical activity, and glycosylated
29 hemoglobin.
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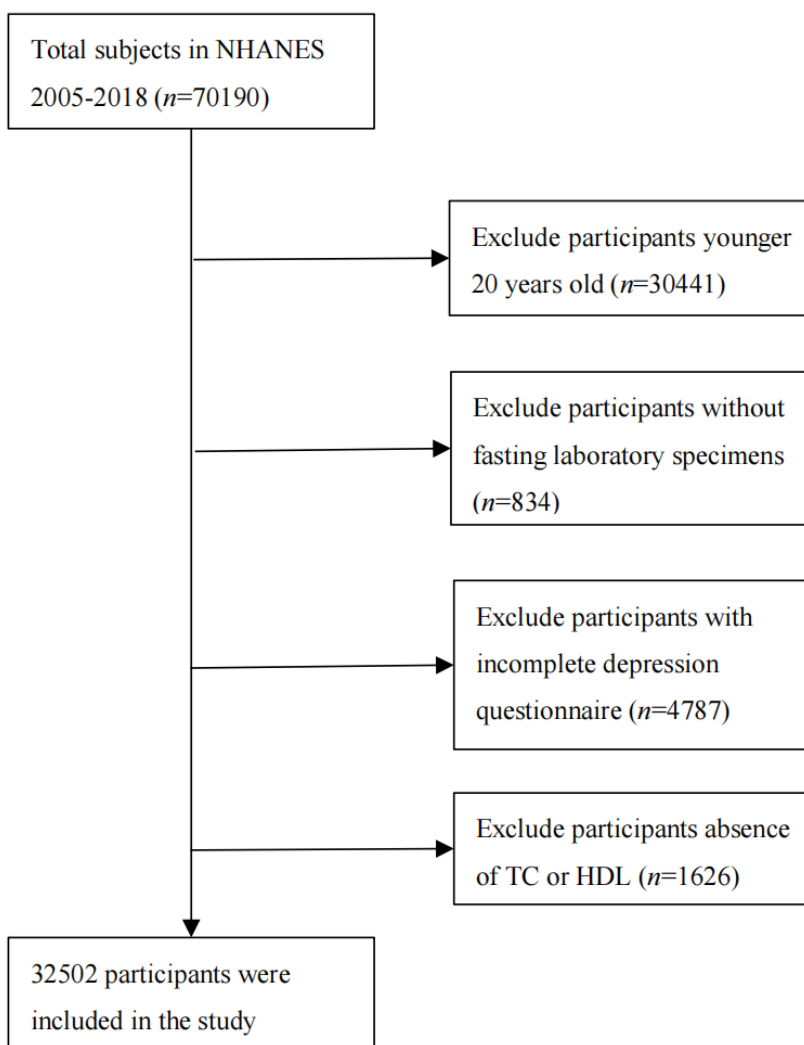
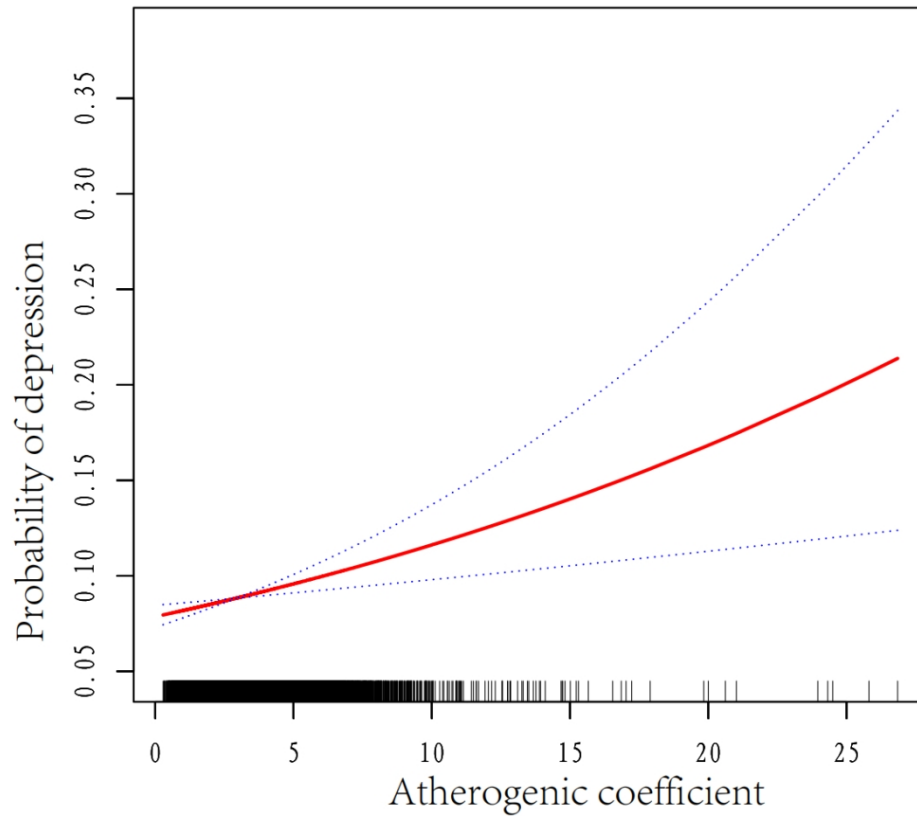


Figure 1. Flowchart for inclusion of study participants.

Flowchart for inclusion of study participants.

114x140mm (200 x 200 DPI)



Association between AC and depression in US adults (n=4759). The black vertical line on the horizontal axis represents the caffeine distribution, the red line represents the best fit, and the difference between the dashed lines represents the 95% confidence interval. The data was adjusted for age, sex, race/ethnicity, body mass index, poverty-income ratio, educational level, marital status, hypertension, diabetes mellitus, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin.

152x152mm (200 x 200 DPI)

Table S1. Missing covariates of study participants ($n = 32502$).

Variable	Number of patients (% missing)
Age	0 (0%)
Sex	0 (0%)
Race/ethnicity	0 (0%)
Educational level	23 (0.07%)
Marital status	16 (0.04%)
Poverty-income ratio	2767 (8.51%)
Body mass index	297 (0.91%)
Alcohol intake	4661 (14.34%)
Smoking status	17 (0.05%)
Physical activity	4102 (12.62%)
Hypertension	0 (0%)
Diabetes mellitus	589 (1.81%)
Glycosylated hemoglobin	58 (0.18%)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7-10 7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	7 7
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between atherogenic coefficient and depression in US adults: a cross-sectional study with data from National Health and Nutrition Examination Survey 2005-2018

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health services research
Keywords:	Risk Factors, Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Lipid disorders < DIABETES & ENDOCRINOLOGY

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4 **Association between atherogenic coefficient and depression in US**
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6 **adults: a cross-sectional study with data from National Health and**
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ABSTRACT

Objective: The pathogenesis of depression is related to immune inflammatory response. AC is an important indicator of lipid abnormalities, which can lead to immune inflammatory responses. However, no study has investigated the relationship between AC and depression in adult Americans. Therefore, we investigated this relationship.

Design: This study used a cross-sectional design.

Setting: The National Health and Nutrition Examination Survey (2005-2018) data were used for this study.

Participants: A total of 32502 participants aged 20 years or older who had complete information for AC and depression were included in this study.

Primary and secondary outcome measures: Depressive symptoms were assessed using the nine-item version of the Patient Health Questionnaire (PHQ-9), with a cutoff point of 9/10 indicating likely depression cases. Weighted logistic regression analyses and the smooth curve fittings were performed to explore the association between AC and depression.

Results: After adjusting for potential confounders, a single unit increase in AC was associated with a 3% increase in the prevalence of depression (hazard ratio =1.03, 95% confidence interval =1.00-1.06, $P = 0.039$). The relationship between AC and depression was more obvious in females.

Conclusions: The AC is positively associated with depression.

Strengths and Limitations:

- The quality and scale of the National Health and Nutrition Examination Survey database ensured our results' statistical power and reliability.
- A wide range of sociodemographic, lifestyle, and physical health covariates were adjusted to reduce residual confounding.
- Its cross-sectional design limited this study, and no causal relationships could be determined.
- The PHQ-9 is a proven, simple, and effective tool for identifying the severity of depressive symptoms, but it is not a diagnostic tool for major depressive disorder (MDD).

INTRODUCTION

Depression is a clinically common emotional state characterized by persistent sadness or inability to experience pleasure, accompanied by deficits in daily functioning [1].

In 2008, the World Health Organization (WHO) ranked major depression as the third leading cause of the global disease burden and projected that it would be the number one cause by 2030 [2]. More than 300 million people worldwide suffer from major depressive disorder (MDD) [3], affecting about 8% of adults in the US [4].

Depression can cause various adverse events, seriously endangering lives and global health [5,6]. Current antidepressant treatments are effective, but there are many side effects; for example, antidepressants may increase suicidal thoughts in some people [7]. Evidence supports screening for depression and providing early intervention [8]. Therefore, it is necessary to explore the factors related to depression.

Abnormal lipid metabolism leads to many pathological changes. Firstly, activation of the pro-inflammatory response leads to a decrease in high-density lipoprotein (HDL) and phospholipids and a compensatory increase in phospholipid-rich low-density lipoprotein (LDL), which in turn slows total cholesterol (TC) metabolism and affects neurotransmitters and neural circuits [9]. However, cytokine signaling in adipose tissue, particularly tumor necrosis factor (TNF), promotes metabolic dysregulation [10]. In addition, some studies have shown that changes in circulating lipid concentrations may be associated with depression [11]. Abnormal lipids are involved in the formation of atherosclerosis. The pathogenesis of atherosclerosis is based on the lipid theory, and the explanation is related to excess cholesterol being the sole cause of lipid deposition in the arterial wall [12]. Atherosclerosis can cause cardiovascular disease (CVD), stroke, etc., often co-morbidities with depression.

The atherogenic coefficient (AC) is an important index for assessing the degree of atherosclerosis, calculated as $(TC - HDL)/HDL$ [13]. Nunes et al. found that AC was elevated in patients with MDD and bipolar disorder [14]. AC and depression can be controlled using statins and other cardiovascular drugs [15,16].

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4 Exploring the role of AC in depression may be beneficial for treating
5 depression and its complications. Therefore, we used data from the National Health
6 and Nutrition Examination Survey (NHANES) database to explore the association of
7 AC with depression in adults.
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11 12 13 14 **METHODS**

15 16 **Study design and participants**

17 Data of the participants in this study were obtained from the NHANES database, a
18 major program conducted by the Centers for Disease Control and Prevention (CDC)
19 to assess the health and nutritional status of 5,000 adults and children in the US
20 annually [17]. The NHANES database contains demographic, dietary, examination,
21 laboratory, and questionnaire data. The National Center for Health Statistics (NCHS)
22 Research Ethics Review Board (ERB) authorized the NHANES study protocols.
23 Further information regarding the NHANES data can be obtained from its official
24 website (<http://www.cdc.gov/nchs/nhanes.htm>).
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33 Participants in our study were screened according to the following inclusion
34 criteria: 1) aged 20 years or above and 2) participation in laboratory tests on an empty
35 stomach. The exclusion criteria were: 1) incomplete Patient Health Questionnaire-9
36 (PHQ-9) and 2) no data on total cholesterol or high-density lipoprotein levels.
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41 **Assessment of depression**

42 The PHQ-9 is used to assess depression. The PHQ-9 contains nine items that capture
43 the frequency of depressive symptoms: appetite problems, fatigue, sleep difficulties,
44 psychomotor retardation or agitation, concentration problems, lack of interest,
45 depressed mood, feelings of worthlessness, and suicidal ideation. It is now widely
46 accepted as an accurate and reliable method for screening depression [18,19]. Each
47 question is scored from '0' (not at all) to '3' (nearly every day), with a total score of
48 0–27, where a score ≥ 10 is considered clinically relevant depression (CRD) [20].
49 PHQ-9 sensitivity compared with semi-structured diagnostic interviews was greater
50 than previous conventional meta-analyses that combined reference standards. A 10- or
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4 above cutoff score maximized the overall sensitivity and specificity for subgroups
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6 [21].

7 **Assessment of AC**

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9 Fasting blood was drawn from individuals aged ≥ 20 years, and the blood samples
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11 were processed, stored, and shipped to the Johns Hopkins University Lipoprotein
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13 Assay Laboratory at the Ambulator-Testing Center laboratory. HDL levels were
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15 measured directly in the serum. The apolipoprotein B (apo B)-containing lipoproteins
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17 in the specimen were reacted with a blocking reagent that rendered them non-reactive
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19 with the enzymatic cholesterol reagent under the assay conditions. Reagents were
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21 purchased from Roche/Boehringer-Mannheim Diagnostics (Mannheim, Germany).
22
23 The method uses sulfated alpha-cyclodextrin in the presence of Mg^{+2} , which forms
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25 complexes with apoB-containing lipoproteins and polyethylene glycol-coupled
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27 cholesteryl esterase and cholesterol oxidase for HDL cholesterol measurement. HDL
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29 cholesterol data collected from participants in 2005-2006 were adjusted using the
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31 following equation: corrected HDL = (Solomon Park assigned HDL value) \times
32
33 (participant HDL). Total cholesterol was measured enzymatically in the serum or
34
35 plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize
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37 the 3-OH cholesterol group. All the information can be obtained from
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39 <https://wwwn.cdc.gov/Nchs/Nhanes/>.

40 **Assessment of covariates**

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42 Covariates in this study, including body mass index (BMI), alcohol intake, physical
43
44 activity, and glycosylated hemoglobin, were used as continuous variables. BMI was
45
46 measured as weight (kg) divided by height (m) squared with <25.0 kg/m² indicating
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48 normal, 25.0 to <30.0 kg/m² indicating overweight, ≥ 30.0 kg/m² indicating obesity.
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50 Alcohol intake was determined by extracting the mean alcohol intake from the first
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52 and second dietary surveys, considering a single day's intake for participants who
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54 consumed alcohol at least once. Physical activity was self-reported by participants as
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56 either inactive, moderate, or vigorous. The study considered CVD to include coronary
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58 heart disease, congestive heart failure, heart attack, stroke, and angina. Categorical
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60 variables included age (20–40 years, 40–60 years, ≥ 60 years), sex (male or female),

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4 and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American,
5 other Hispanic, or other race/multiple races). The poverty-income ratio (PIR) was
6 defined as the ratio of family income to poverty threshold (<1 indicating an income
7 below the poverty threshold and ≥ 1 indicating an income above the poverty threshold.
8
9 The latter category was further classified into two groups: 1.00 to <2.00 and ≥ 2.00).
10
11 Education level was categorized as high school not completed, high school
12 completed, or high school graduate and some college or associated degrees pursued.
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14 Marital status was defined as married/living with a partner or
15 widowed/divorced/separated/never married. Hypertension (HTN) (defined as systolic
16 blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) was determined
17 using three blood pressure measurements at different times, an existing diagnosis, or
18 evidence of an existing antihypertensive medication regimen. Diabetes mellitus (DM)
19 was defined as either taking glucose-lowering therapies, a glycosylated hemoglobin
20 (HbA1c) concentration of $\geq 6.5\%$, use of anti-diabetic medication, oral glucose
21 tolerance test (OGTT) ≥ 11.1 mmol/L, fasting plasma glucose ≥ 7.0 mmol/L, or
22 random blood glucose ≥ 11.1 mmol/L. Smoking status was categorized as
23 non-smokers (smoked <100 cigarettes in a lifetime), former smoker (not currently
24 smoking but have consumed ≥ 100 cigarettes previously), and current smoker
25 (smoking at least ≥ 100 cigarettes every day or some days). The use of antidepressants,
26 anxiolytics, sedatives, and hypnotics was were divided into use or non-use through
27 questionnaires.
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44 **Statistical analysis**

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46 The main concern was whether AC is associated with depression after adjusting for
47 other factors that may influence depression. Continuous variables are expressed as
48 mean \pm standard deviation, and categorical variables are expressed as percentages.
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50 The weighted χ^2 test was used to compare categorical variables between groups, a
51 one-way analysis of variance was used to compare normally distributed variables
52 between groups, and the Kruskal-Wallis H test was used to compare variables with a
53 skewed distribution between groups. Weighted multivariate logistic regression
54 analysis evaluated the independent association between AC and depression. The
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4 participants were categorized into four groups based on AC: < 1.9310 , 1.9310 to $<$
5 2.6695 , 2.6695 to < 3.6430 , and ≥ 3.6430 . We used three levels of adjustment: Model
6 1 was adjusted for age, sex, and race/ethnicity; Model 2 was adjusted for the variables
7 in Model 1 plus BMI, PIR, educational level, and marital status; and Model 3 was
8 adjusted for the variables in Model 2 plus HTN, DM, alcohol intake, smoking status,
9 physical activity, and glycosylated hemoglobin. The imputation of missing data was
10 conducted using the missForest R package. This random forest-based technique is
11 highly computationally efficient for high-dimensional data of categorical and
12 continuous predictors [22]. The missing values are presented in the table (Table S1).

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21 All analyses were performed using R software (The R Foundation, Vienna,
22 Austria) and Empower (X&Y Solutions, Boston, MA, USA). Statistical significance
23 was defined as a two-sided P -value < 0.05 .

24 25 26 27 **Patient and public involvement**

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30 None.

31 32 33 34 **RESULTS**

35 36 37 **Participant characteristics**

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39 In this study, 32,502 participants were included (Figure 1). Table 1 shows the
40 characteristics of the participants according to their AC. There were statistically
41 significant differences in age, sex, educational level, race/ethnicity, marital status,
42 PIR, alcohol intake, smoking status, physical activity, BMI, HTN, DM, HbA1c,
43 cholesterol, and HDL between the different AC groups ($P < 0.05$). In addition, there
44 were no significant differences in the use of antidepressants, anxiolytics, sedatives,
45 and hypnotics in participants with CVD ($p > 0.05$). Covariates with $P < 0.05$ in
46 univariate analysis were included for further analysis.

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61 Participants in the lowest AC in Q1 (< 1.9310) were likely to be female,
younger, more educated, married or cohabitating, non-Hispanic White, wealthier, less
physically active, smoked less, consumed more alcohol, had no DM or HTN, higher
HDL levels, lower BMI, lower HbA1c levels, and TC levels.

In contrast, participants with the highest AC in Q4 (>3.6430) were likely to be male, middle-aged, more highly educated, non-Hispanic White, married or cohabitating, wealthier, consumed less alcohol, never smoked, inactive and obese, had HTN, lower HDL levels, higher BMI, higher HbA1c and TC levels.

Table 1. Characteristics of the study population, using National Health and Nutrition Examination Survey data from 2005–2018 (N = 32,502), Weighted

Characteristic	Overall	Atherogenic coefficient quartiles†				p-value
		Q1 (< 1.9310)	Q2 (1.9310 to < 2.6695)	Q3 (2.6695 to < 3.6430)	Q4 (≥ 3.6430)	
Sex (%)						<0.001
Male	48.78 (48.21,49.35)	32.75 (31.33, 34.21)	42.40 (40.95, 43.87)	54.04 (52.56,55.52)	66.36 (65.00,67.70)	
Female	51.22 (50.65, 51.79)	67.25 (65.79, 68.67)	57.60 (56.13, 59.05)	45.96 (44.48, 47.44)	33.64 (32.30, 35.00)	
Age (%)						<0.001
20 to < 40	35.93 (34.76, 37.12)	40.78 (38.93, 42.66)	36.40 (34.73, 38.10)	33.15 (31.58, 34.76)	33.30 (31.69, 34.95)	
40 to <60	37.75 (36.83, 38.67)	29.54 (27.96, 31.18)	35.21 (33.59, 36.87)	40.86 (39.37,42.37)	45.58 (43.89, 47.29)	
≥ 60	26.32 (25.26,27.40)	29.67 (28.04, 31.36)	28.39 (26.74, 30.09)	25.99 (24.53, 27.50)	21.12 (19.78,22.52)	
Educational level (%)						<0.001
<High school	15.44 (14.36, 16.58)	12.40 (11.24, 13.65)	14.04 (12.70, 15.49)	16.18 (14.78, 17.67)	19.24 (17.90, 20.65)	
Completed high school	23.30 (22.35, 24.27)	20.49 (19.12, 21.93)	22.16 (20.82, 23.56)	24.87 (23.59,26.20)	25.75 (24.17, 27.40)	
>High school	61.26 (59.57, 62.92)	67.11 (65.08, 69.08)	63.80 (61.69, 65.86)	58.95 (56.99, 60.89)	55.02 (52.92, 57.09)	
Race/ethnicity (%)						<0.001
Non-Hispanic White	68.41 (65.86, 70.86)	69.02 (66.42, 71.51)	68.41 (65.87, 70.84)	68.23 (65.19, 71.72)	67.98 (65.01, 70.81)	
Non-Hispanic Black	10.50 (9.27,11.88)	13.76 (12.07, 15.64)	11.32 (9.98, 12.81)	9.65 (8.42, 11.03)	7.20 (6.22, 8.32)	
Mexican American	8.46 (7.22, 9.89)	6.06 (5.10, 7.18)	7.53 (6.34, 8.93)	9.50 (8.04, 11.20)	10.82 (9.06, 12.86)	
Other Hispanic	5.44 (4.65,6.35)	4.27 (3.54, 5.13)	5.22 (4.40, 6.18)	5.83 (4.87, 6.97)	6.47 (5.42, 7.70)	
Other races/multiple races	7.18 (6.50, 7.93)	6.89 (6.08, 7.81)	7.52 (6.63, 8.51)	6.79 (5.96, 7.73)	7.54 (6.67, 8.50)	
Marital status (%)						<0.001
Married/Living with a partner	64.04 (62.84, 65.22)	59.25 (57.29, 61.17)	62.92 (61.31, 64.54)	66.06 (64.48, 67.61)	68.04 (66.58,69.46)	
Widowed/Divorced/Separated/Never married	35.96 (34.78, 37.16)	40.75 (38.83, 42.71)	37.08 (35.49, 38.69)	33.94 (32.39, 35.52)	31.96 (30.54, 33.42)	
PIR (%)						<0.001
< 1.00	13.58 (12.64, 14.57)	12.69 (11.51, 13.97)	13.36 (12.18, 14.64)	12.77 (11.70, 13.92)	15.51 (14.13, 17.00)	
1.00 to <2.00	20.31 (19.33, 21.32)	18.88 (17.52, 20.31)	19.48 (18.36, 20.65)	21.07 (19.63, 22.60)	21.83 (20.18, 23.57)	
≥ 2.00	66.12 (64.45, 67.74)	68.44 (66.44, 70.37)	67.16 (65.18, 69.08)	66.15 (64.30, 67.96)	62.66 (60.14, 65.12)	
Alcohol intake (g/day)	9.38 (8.90,9.87)	12.33 (11.43, 13.24)	8.91 (8.22, 9.61)	7.84 (7.19, 8.49)	8.43 (7.62, 9.25)	<0.001

Smoking status (%)									<0.001
Non-smoker	54.76 (53.63, 55.88)	58.23 (56.66, 59.78)	56.97 (55.26, 58.66)	54.94 (53.42, 56.45)	48.79 (47.25, 50.33)				
Former smoker	25.13 (24.28, 26.00)	24.55 (23.30, 25.85)	24.60 (23.23, 26.02)	26.12 (24.65, 27.66)	25.26 (24.00, 26.56)				
Current smoker	20.11 (19.24, 21.01)	17.22 (16.03, 18.48)	18.44 (17.19, 19.75)	18.94 (17.85, 20.08)	25.95 (24.45, 27.51)				
Physical activity (%)									<0.001
Inactive	45.81 (44.18, 47.45)	39.32 (36.97, 41.72)	44.08 (41.77, 46.42)	47.93 (46.10, 49.77)	52.15 (50.11, 54.17)				
Moderate	28.01 (26.94, 29.11)	27.48 (25.78, 29.25)	28.01 (26.30, 29.78)	29.11 (27.52, 30.76)	27.43 (25.81, 29.11)				
Vigorous	8.05 (7.55, 8.59)	8.86 (7.84, 9.99)	8.74 (7.74, 9.85)	7.25 (6.40, 8.20)	7.36 (6.37, 8.48)				
Both moderate and vigorous	18.13 (116.98, 19.34)	24.34 (22.46, 26.33)	19.17 (17.54, 20.93)	15.71 (4.27, 17.25)	13.07 (11.83, 14.42)				
BMI (kg/m ²)	29.10 (28.94, 29.26)	26.12 (25.94, 26.30)	28.70 (28.49, 28.90)	30.28 (30.04, 30.52)	31.38 (31.17, 31.59)				<0.001
HTN (%)	38.20 (37.15, 39.25)	32.90 (31.30, 34.54)	36.35 (34.76, 37.96)	40.33 (38.70, 41.98)	43.34 (41.78, 44.93)				<0.001
DM (%)	14.38 (13.77, 15.02)	11.47 (10.59, 12.40)	13.43 (12.48, 14.45)	14.90 (13.73, 16.15)	17.76 (16.69, 18.88)				<0.001
CVD (%)	8.73 (8.25, 9.22)	9.42 (8.55, 10.37)	8.75 (7.97, 9.60)	8.44 (7.65, 9.30)	8.28 (7.45, 9.20)				0.207
Depression (%)	7.69 (7.24, 8.17)	6.48 (5.77, 7.26)	7.16 (6.30, 8.12)	8.27 (7.46, 9.16)	8.89 (8.16, 9.68)				<0.001
HbA1c (%)	5.61 (5.60, 5.63)	5.44 (5.42, 5.47)	5.55 (5.53, 5.57)	5.64 (5.61, 5.67)	5.82 (5.79, 5.86)				<0.001
Cholesterol (mmol/L)	5.02 (5.00, 5.05)	4.46 (4.43, 4.50)	4.77 (4.74, 4.80)	5.10 (5.07, 5.13)	5.77 (5.73, 5.80)				<0.001
HDL cholesterol (mmol/L)	1.38 (1.37, 1.39)	1.82 (1.80, 1.84)	1.45 (1.44, 1.46)	1.24 (1.24, 1.25)	1.01 (1.00, 1.02)				<0.001
Antidepressants (%)	13.17 (12.52, 13.84)	12.65 (11.66, 13.70)	13.76 (12.67, 14.93)	13.25 (12.25, 14.33)	13.01 (11.83, 14.28)				0.477
Anxiolytics, sedatives, and hypnotics (%)	6.78 (6.33, 7.27)	7.29 (6.54, 8.12)	6.78 (6.07, 7.56)	6.31 (5.56, 7.15)	6.75 (5.93, 7.68)				0.339

For continuous variables: survey-weighted mean (95% CI), the *p*-value was by survey-weighted linear regression (svyglm). For categorical variables: survey-weighted percentage (95% CI), the *p*-value was by survey-weighted Chi-square test (svytable).

Abbreviations: DM, diabetes mellitus; CVD: cardiovascular disease; BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HTN, hypertension; PIR, poverty-income ratio (ratio of family income to poverty threshold); SD, standard deviation

Association between AC and depression

In the fully adjusted model, we observed a linear relationship between AC and depression (Figure 2). The results of the weighted multivariate logistic regression analysis are presented in Table 2. AC was positively correlated with depression in the crude model (odds ratio [OR]= 1.08, 95% confidence interval [CI]:1.06-1.11, *P* <0.001). A significant association between AC and depression was detected in Models 1-3 after adjusting for confounders. In Model 3, all variables were adjusted; for every 1 unit increase in AC, the incidence of depression increased by 3% (OR = 1.03, 95% CI = 1.00–1.06, *P* = 0.039).

Table 2. Associations of the atherogenic coefficient with depression (n = 32,502), Weighted.

	Crude Modela		Model 1b		Model 2c		Model 3d	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Per 1 increase	1.08 (1.06,1.11)	<0.001	1.13 (1.10,1.16)	<0.001	1.07 (1.04,1.10)	<0.001	1.03 (1.00,1.06)	0.039
Quartiles								
Q1 (AC: < 1.9310)	Reference [1]		Reference [1]		Reference [1]		Reference [1]	
Q2 (AC: 1.9310 to < 2.6695)	1.11 (0.96,1.30)	0.166	1.18 (1.01,1.38)	0.040	1.07 (0.91,1.25)	0.431	1.04 (0.89,1.22)	0.589
Q3 (AC: 2.6695 to < 3.6430)	1.30 (1.11,1.53)	0.001	1.48 (1.26,1.74)	<0.001	1.24 (1.07,1.45)	0.006	1.18 (1.02,1.38)	0.034
Q4 (AC: ≥ 3.6430)	1.41 (1.22,1.62)	<0.001	1.75 (1.50,2.03)	<0.001	1.32 (1.14,1.54)	<0.001	1.15 (0.99,1.33)	0.074
<i>p</i> for trend	<0.001		<0.001		<0.001		0.040	

Abbreviations: AC, atherogenic coefficient.

aModel 1: Adjusted for age, sex, and race/ethnicity.

bModel 2: Adjusted for the variables in Model 1 plus body mass index, poverty-income ratio, educational level, and marital status.

cModel 3: Adjusted for the variables in Model 2 plus hypertension, diabetes mellitus, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin.

After adjusting for age, sex, race/ethnicity, BMI, PIR, educational level, marital status, HTN, DM, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin compared with participants in the first quartile (AC < 1.9310), the second group (1.9310 to < 2.6695, OR = 1.04, 95% CI = 0.89– 1.22, *P* = 0.589), the third group (2.6695 to < 3.6430, OR = 1.18, 95% CI = 1.02– 1.38, *P* = 0.034), and the fourth group (≥ 3.6430, OR = 1.15, 95% CI = 0.99– 1.33, *P* = 0.074) had an increased prevalence of depression (*P* for trend was significant in all the models).

Furthermore, regarding the interaction between sex and the relationship between AC and depression, the relationship was more significant in females (OR = 1.07, 95% CI = 1.02–1.12, *P* for interaction = 0.027) (Table 3).

Table 3. Subgroup analysis of the effect of the atherogenic coefficient on depression (n = 32502), Weight.

Subgroup	Number of	OR (95% CI)	<i>P</i> for
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	participants		interaction
Sex, n (%)			0.027
Male	15954	1.05 (1.01, 1.10)	
Female	16548	1.07 (1.02, 1.12)	
Age, n (%)			0.375
20 – < 40	10857	1.07 (1.02, 1.12)	
40 – < 60	10632	1.04 (0.99, 1.09)	
≥ 60	11013	1.04 (0.97, 1.11)	
Race/ethnicity, n (%)			0.196
Non-Hispanic White	14112	1.03 (0.99, 1.08)	
Non-Hispanic Black	6713	1.06 (0.98, 1.15)	
Mexican American	5174	1.05 (0.97, 1.14)	
Other Hispanic	3109	1.12 (1.06, 1.19)	
Other race/multiple races	3394	1.10 (0.96, 1.26)	
BMI, kg/m ² , mean (SD)			0.212
Low	10729	1.08 (1.00, 1.17)	
Middle	10733	1.06 (1.01, 1.12)	
High	10743	1.03 (0.99, 1.08)	
Hypertension, n (%)			0.949
Yes	13940	1.04 (1.00, 1.08)	
No	18562	1.06 (1.01, 1.12)	
DM, n (%)			0.670
Yes	6152	1.03 (0.98, 1.08)	
No	25761	1.07 (1.03, 1.11)	

Abbreviations: BMI, body mass index (calculated as weight, in kilograms, divided by the square of height, in meters); DM, diabetes mellitus; HTN, hypertension

DISCUSSION

This cross-sectional study showed an association between AC and depression in adults in the United States. After adjusting for covariates, a positive linear relationship was found between AC and depression.

The details of the mechanism explaining the relationship between AC and depression need to be further explored, and there may be several possible explanations. Lipids and the immune system interact with one another and have a regulatory effect on each other. Dysregulated inflammation promotes susceptibility to depression [23]. Studies have shown that inflammatory cytokines produced in the periphery enter the cells of the central nervous system and can affect neurotransmitters and neural circuits, producing behavioral symptoms of depression

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4 [24]. When T lymphocytes are activated, they not only participate in immune
5 inflammation but also directly contribute to the development of depression when
6 functionally impaired [25,26]. Lipid peroxidation and oxidation-specific epitopes are
7 formed, and the levels of antioxidants such as glutathione, glutathione peroxidase, and
8 coenzyme Q10 are reduced, resulting in or aggravating oxidative stress [27,28].
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14 When lipids are abnormal, the inflammatory, oxidative, and nitrosative
15 (IO&NS) pathway is further activated [29]. At this time, the increase in binding
16 globin and high-sensitivity C-reactive protein (CRP) is accompanied by a significant
17 increase in interleukin-6 (IL-6), tumor necrosis factor- α , interferon- γ , other
18 pro-inflammatory cytokines, and immune inflammation [30]. These factors lead to
19 defects in serotonin and melatonin through the kynurenine pathway, often considered
20 one of the main causes of depression [31]. Activation of the IO&NS pathway leads to
21 mitochondrial and subsequent cellular dysfunction [32]. Previous studies have linked
22 mitochondrial dysfunction in various brain regions to depression [33].
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32 Statins have also been shown to have antidepressant effects when
33 co-prescribed with antidepressants [34]. Lowering the AC index of patients with
34 mood disorders improves CVD outcomes [35]. CVD is a heart and blood vessel
35 disease characterized by myocardial infarction, angina pectoris, heart failure, heart
36 attack, and stroke [36]. Longer exposure to depression is associated with significantly
37 increased CVD risk [37]. Factors contributing to the link between depression and
38 cardiac outcome may include alterations in the autonomic nervous system, platelet
39 receptors and function, coagulopathic factors, pro-inflammatory cytokines,
40 endothelial function, neurohormonal factors, and genetic linkages [38]. At the same
41 time, patient compliance with antidepressant treatment is relatively poor [39].
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Atherosclerosis is a chronic vascular inflammatory disease associated with oxidative
stress and endothelial dysfunction [40]. Atherosclerosis is the underlying cause of
CVD, and AC is a major indicator of atherosclerosis [41]. Our results suggest that AC
may play a role in depression. AC may indicate the relationship between CVD and
depression and a potential target and marker for treating depression or depression
combined with CVD. The relevant mechanisms remain to be explored further.

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4 Our study found increased odds of depression with increased AC in adults,
5 demonstrating that controlling AC may be beneficial for preventing depression. Sex
6 may affect this relationship. In the subgroup analysis (Table 3), we found a stronger
7 relationship between AC and depression in females. The synergistic effect of estrogen
8 on cognitive and emotional functions may underlie the association between ovarian
9 hormone fluctuations and depression in females [42]. The induction of indoleamine 2,
10 3-dioxygenase, and deleterious effects of tryptophan catabolizing metabolites
11 (TRYCATs) play a role in the pathophysiology of depression. Activation of IDO
12 decreases plasma tryptophan levels and increases TRYCAT synthesis in depressed
13 individuals. Females showed more IDO activation and TRYCAT production after
14 immune challenge than males [43]. Therefore, this sex difference in immune
15 dysregulation may contribute to higher levels of anxiety and depression experienced
16 by females.
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29 This study has some limitations. First, this was a cross-sectional study;
30 therefore, we could not determine a causal relationship between AC and depression.
31 Second, the PHQ-9 is a proven, simple, and effective tool for identifying the severity
32 of depressive symptoms, but it is not a diagnostic tool for MDD. Third, the
33 relationship we studied may have been influenced by other confounding factors,
34 which we have not adjusted. Fourth, the differences in demographics and population
35 characteristics in the United States may limit the generalizability of the findings to
36 other countries or regions.
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48 CONCLUSIONS

49 Our research shows that higher AC levels in American adults are positively related to
50 a higher prevalence of depression. Further studies are required to explore the
51 underlying mechanisms and potential benefits of controlling AC levels in patients
52 with depression.
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6

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8 J Yin; validation, H Sun, Y Liu and J Yang; formal analysis, L Zhang, J Yin, and H Sun;
9 investigation, L Zhang; resources, L Zhang; data curation, H Sun; writing—original draft
10 preparation, L Zhang; writing—review and editing, Y Liu and J Yang; visualization, J Yin;
11 supervision, Y Liu and J Yang; project administration, L Zhang. All authors have read and
12 agreed to the published version of the manuscript.
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25 **Data Sharing Statement:** The datasets generated and/or analyzed during the current study
26 are available in the NHANES repository [<https://www.cdc.gov/nchs/nhanes/>].
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FIGURE LEGENDS

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4 **Figure 1.** Flowchart for inclusion of study participants.

5 **Figure 2.** Association between AC and depression in US adults (n=4759). The black
6 vertical line on the horizontal axis represents the AC distribution, the red line
7 represents the best fit, and the difference between the dashed lines represents the 95%
8 confidence interval. The data was adjusted for age, sex, race/ethnicity, body mass
9 index, poverty-income ratio, educational level, marital status, hypertension, diabetes
10 mellitus, alcohol intake, smoking status, physical activity, and glycosylated
11 hemoglobin.
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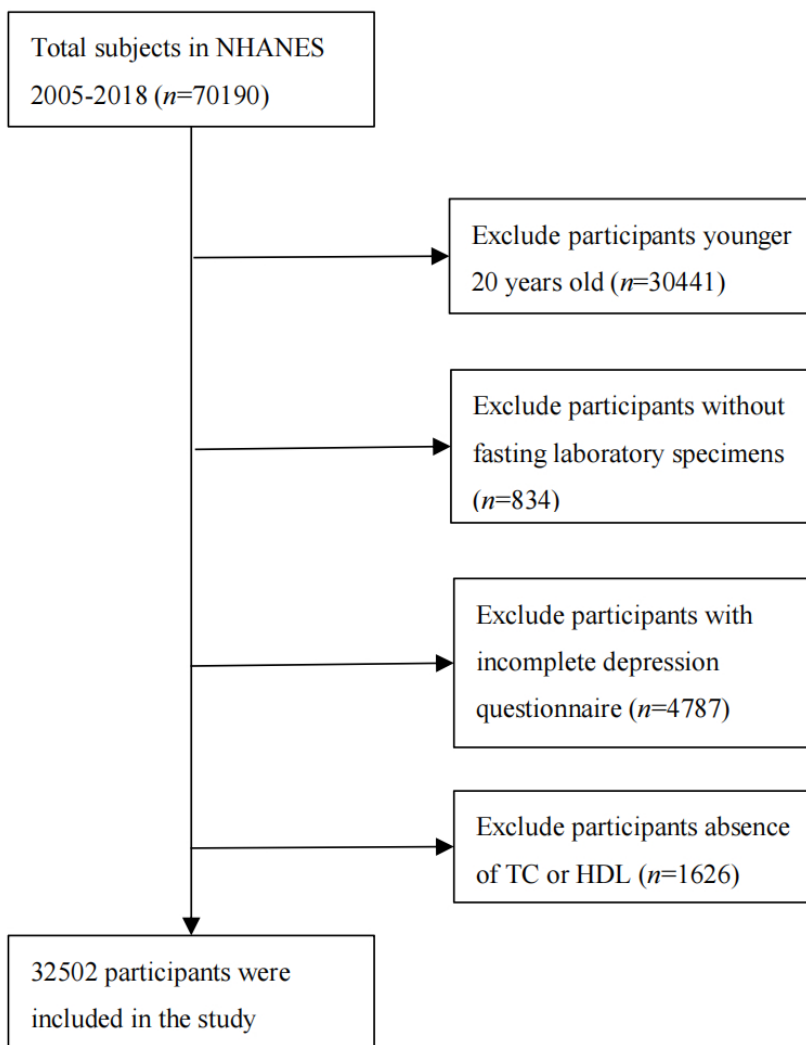
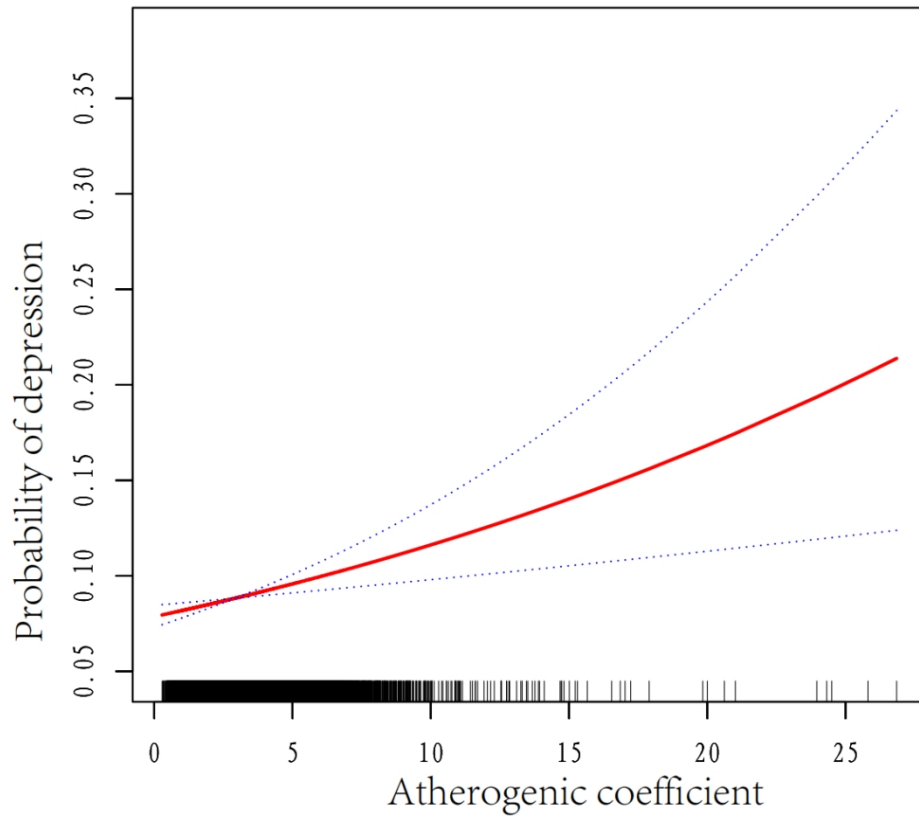


Figure 1. Flowchart for inclusion of study participants.

Flowchart for inclusion of study participants.

114x140mm (200 x 200 DPI)



Association between AC and depression in US adults (n=4759). The black vertical line on the horizontal axis represents the caffeine distribution, the red line represents the best fit, and the difference between the dashed lines represents the 95% confidence interval. The data was adjusted for age, sex, race/ethnicity, body mass index, poverty-income ratio, educational level, marital status, hypertension, diabetes mellitus, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin.

152x152mm (200 x 200 DPI)

Table S1. Missing covariates of study participants (n = 32502)

Variable	Number of patients (% missing)
Age	0 (0%)
Sex	0 (0%)
Race/ethnicity	0 (0%)
Educational level	23 (0.07%)
Marital status	16 (0.04%)
Poverty-income ratio	2767 (8.51%)
Body mass index	297 (0.91%)
Alcohol intake	4661 (14.34%)
Smoking status	17 (0.05%)
Physical activity	4102 (12.62%)
Hypertension	0 (0%)
Diabetes mellitus	589 (1.81%)
Glycosylated hemoglobin	58 (0.18%)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	4
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between atherogenic coefficient and depression in US adults: a cross-sectional study with data from National Health and Nutrition Examination Survey 2005-2018

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Primary Subject Heading:	Mental health
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Keywords:	Risk Factors, Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Lipid disorders < DIABETES & ENDOCRINOLOGY

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4 **Association between atherogenic coefficient and depression in US**
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6 **adults: a cross-sectional study with data from National Health and**
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11 **Lu Zhang^{a1}, Jiahui Yin^{b1}, Haiyang Sun^{c1}, Jiguo Yang^{d*}, Yuanxiang Liu^{e*}**

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ABSTRACT

Objective: The pathogenesis of depression is related to immune inflammatory response. AC is an important indicator of lipid abnormalities, which can lead to immune inflammatory responses. However, no study has investigated the relationship between AC and depression in adult Americans. Therefore, we investigated this relationship.

Design: This study used a cross-sectional design.

Setting: The National Health and Nutrition Examination Survey (2005-2018) data were used for this study.

Participants: A total of 32502 participants aged 20 years or older who had complete information for AC and depression were included in this study.

Primary and secondary outcome measures: Depressive symptoms were assessed using the nine-item version of the Patient Health Questionnaire (PHQ-9), with a cutoff point of 9/10 indicating likely depression cases. Weighted logistic regression analyses and the smooth curve fittings were performed to explore the association between AC and depression.

Results: After adjusting for potential confounders, a single unit increase in AC was associated with a 3% increase in the prevalence of depression (hazard ratio =1.03, 95% confidence interval =1.00-1.06, $P = 0.039$). The relationship between AC and depression was more obvious in females.

Conclusions: The AC is positively associated with depression.

Strengths and Limitations:

- The quality and scale of the National Health and Nutrition Examination Survey database ensured our results' statistical power and reliability.
- A wide range of sociodemographic, lifestyle, and physical health covariates were adjusted to reduce residual confounding.
- Its cross-sectional design limited this study, and no causal relationships could be determined.
- The PHQ-9 is a proven, simple, and effective tool for identifying the severity of depressive symptoms, but it is not a diagnostic tool for major depressive disorder (MDD).

INTRODUCTION

Depression is a clinically common emotional state characterized by persistent sadness or inability to experience pleasure, accompanied by deficits in daily functioning [1].

In 2008, the World Health Organization (WHO) ranked major depression as the third leading cause of the global disease burden and projected that it would be the number one cause by 2030 [2]. More than 300 million people worldwide suffer from major depressive disorder (MDD) [3], affecting about 8% of adults in the US [4].

Depression can cause various adverse events, seriously endangering lives and global health [5,6]. Current antidepressant treatments are effective, but there are many side effects; for example, antidepressants may increase suicidal thoughts in some people [7]. Evidence supports screening for depression and providing early intervention [8]. Therefore, it is necessary to explore the factors related to depression.

Abnormal lipid metabolism leads to many pathological changes. Firstly, activation of the pro-inflammatory response leads to a decrease in high-density lipoprotein (HDL) and phospholipids and a compensatory increase in phospholipid-rich low-density lipoprotein (LDL), which in turn slows total cholesterol (TC) metabolism and affects neurotransmitters and neural circuits [9]. However, cytokine signaling in adipose tissue, particularly tumor necrosis factor (TNF), promotes metabolic dysregulation [10]. In addition, some studies have shown that changes in circulating lipid concentrations may be associated with depression [11]. Abnormal lipids are involved in the formation of atherosclerosis. The pathogenesis of atherosclerosis is based on the lipid theory, and the explanation is related to excess cholesterol being the sole cause of lipid deposition in the arterial wall [12]. Atherosclerosis can cause cardiovascular disease (CVD), stroke, etc., often co-morbidities with depression.

The atherogenic coefficient (AC) is an important index for assessing the degree of atherosclerosis, calculated as $(TC - HDL)/HDL$ [13]. Nunes et al. found that AC was elevated in patients with MDD and bipolar disorder [14]. AC and depression can be controlled using statins and other cardiovascular drugs [15,16].

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4 Exploring the role of AC in depression may be beneficial for treating
5 depression and its complications. Therefore, we used data from the National Health
6 and Nutrition Examination Survey (NHANES) database to explore the association of
7 AC with depression in adults.
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11 12 13 14 **METHODS**

15 16 **Study design and participants**

17 Data of the participants in this study were obtained from the NHANES database, a
18 major program conducted by the Centers for Disease Control and Prevention (CDC)
19 to assess the health and nutritional status of 5,000 adults and children in the US
20 annually [17]. The NHANES database contains demographic, dietary, examination,
21 laboratory, and questionnaire data. The National Center for Health Statistics (NCHS)
22 Research Ethics Review Board (ERB) authorized the NHANES study protocols.
23 Further information regarding the NHANES data can be obtained from its official
24 website (<http://www.cdc.gov/nchs/nhanes.htm>).
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33 Participants in our study were screened according to the following inclusion
34 criteria: 1) aged 20 years or above and 2) participation in laboratory tests on an empty
35 stomach. The exclusion criteria were: 1) incomplete Patient Health Questionnaire-9
36 (PHQ-9) and 2) no data on TC or HDL cholesterol levels.
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41 **Assessment of depression**

42 The PHQ-9 is used to assess depression. The PHQ-9 contains nine items that capture
43 the frequency of depressive symptoms: appetite problems, fatigue, sleep difficulties,
44 psychomotor retardation or agitation, concentration problems, lack of interest,
45 depressed mood, feelings of worthlessness, and suicidal ideation. It is now widely
46 accepted as an accurate and reliable method for screening depression [18,19]. Each
47 question is scored from '0' (not at all) to '3' (nearly every day), with a total score of
48 0–27, where a score ≥ 10 is considered clinically relevant depression (CRD) [20].
49 PHQ-9 sensitivity compared with semi-structured diagnostic interviews was greater
50 than previous conventional meta-analyses that combined reference standards. A 10- or
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4 above cutoff score maximized the overall sensitivity and specificity for subgroups
5 [21].
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7 **Assessment of AC**

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9 Fasting blood was drawn from individuals aged ≥ 20 years, and the blood samples
10 were processed, stored, and shipped to the Johns Hopkins University Lipoprotein
11 Assay Laboratory at the Ambulator-Testing Center laboratory. HDL cholesterol levels
12 were measured directly in the serum. The apolipoprotein B (apo B)-containing
13 lipoproteins in the specimen were reacted with a blocking reagent that rendered them
14 non-reactive with the enzymatic cholesterol reagent under the assay conditions.
15 Reagents were purchased from Roche/Boehringer-Mannheim Diagnostics
16 (Mannheim, Germany). The method uses sulfated alpha-cyclodextrin in the presence
17 of Mg^{+2} , which forms complexes with apoB-containing lipoproteins and polyethylene
18 glycol-coupled cholesteryl esterase and cholesterol oxidase for HDL cholesterol
19 measurement. HDL cholesterol data collected from participants in 2005-2006 were
20 adjusted using the following equation: corrected HDL = (Solomon Park assigned
21 HDL value) \times (participant HDL). TC was measured enzymatically in the serum or
22 plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize
23 the 3-OH cholesterol group. All the information can be obtained from
24 <https://wwwn.cdc.gov/Nchs/Nhanes/>.
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40 **Assessment of covariates**

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42 Covariates in this study, including body mass index (BMI), alcohol intake, and
43 glycosylated hemoglobin (HbA1c), were used as continuous variables. BMI was
44 measured as weight (kg) divided by height (m) squared with <25.0 kg/m² indicating
45 normal, 25.0 to <30.0 kg/m² indicating overweight, ≥ 30.0 kg/m² indicating obesity.
46 Alcohol intake was determined by extracting the mean alcohol intake from the first
47 and second dietary surveys, considering a single day's intake for participants who
48 consumed alcohol at least once. Physical activity was self-reported by participants as
49 either inactive, moderate, or vigorous. Categorical variables included age (20–40
50 years, 40–60 years, ≥ 60 years), sex (male or female), and race/ethnicity (non-Hispanic
51 white, non-Hispanic black, Mexican American, other Hispanic, or other race/multiple
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4 races). The poverty-income ratio (PIR) was defined as the ratio of family income to
5 poverty threshold (<1 indicating an income below the poverty threshold and ≥ 1
6 indicating an income above the poverty threshold. The latter category was further
7 classified into two groups: 1.00 to <2.00 and ≥ 2.00). Education level was categorized
8 as high school not completed, high school completed, or high school graduate and
9 some college or associated degrees pursued. Marital status was defined as
10 married/living with a partner or widowed/divorced/separated/never married.
11 Hypertension (HTN) (defined as systolic blood pressure ≥ 140 mmHg or diastolic
12 blood pressure ≥ 90 mmHg) was determined using three blood pressure measurements
13 at different times, an existing diagnosis, or evidence of an existing antihypertensive
14 medication regimen. Diabetes mellitus (DM) was defined as either taking
15 glucose-lowering therapies, HbA1c concentration of $\geq 6.5\%$, use of anti-diabetic
16 medication, oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L, fasting plasma glucose
17 ≥ 7.0 mmol/L, or random blood glucose ≥ 11.1 mmol/L. Smoking status was
18 categorized as non-smokers (smoked <100 cigarettes in a lifetime), former smoker
19 (not currently smoking but have consumed ≥ 100 cigarettes previously), and current
20 smoker (smoking at least ≥ 100 cigarettes every day or some days).
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36 **Statistical analysis**

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38 The main concern was whether AC is associated with depression after adjusting for
39 other factors that may influence depression. Continuous variables are expressed as
40 mean \pm standard deviation, and categorical variables are expressed as percentages.
41 The weighted χ^2 test was used to compare categorical variables between groups, a
42 one-way analysis of variance was used to compare normally distributed variables
43 between groups, and the Kruskal-Wallis H test was used to compare variables with a
44 skewed distribution between groups. Variance inflation factors were used to test
45 multi-collinearity. Weighted multivariate logistic regression analysis evaluated the
46 independent association between AC and depression. The participants were
47 categorized into four groups based on AC: < 1.9310 , 1.9310 to < 2.6695 , 2.6695 to $<$
48 3.6430 , and ≥ 3.6430 . We used three levels of adjustment: Model 1 was adjusted for
49 age, sex, and race/ethnicity; Model 2 was adjusted for the variables in Model 1 plus
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4 BMI, PIR, educational level, and marital status; and Model 3 was adjusted for the
5 variables in Model 2 plus HTN, DM, alcohol intake, smoking status, physical activity,
6 and HbA1c. The imputation of missing data was conducted using the missForest R
7 package. This random forest-based technique is highly computationally efficient for
8 high-dimensional data of categorical and continuous predictors [22]. The missing
9 values are presented in the table (Table S1).
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15 All analyses were performed using R software (The R Foundation, Vienna,
16 Austria) and Empower (X&Y Solutions, Boston, MA, USA). Statistical significance
17 was defined as a two-sided *P*-value <0.05.
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21 **Patient and public involvement**

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24 None.
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29 **RESULTS**

30 **Participant characteristics**

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32 In this study, 32,502 participants were included (Figure 1). Table 1 shows the
33 characteristics of the participants according to their AC. There were statistically
34 significant differences in age, sex, educational level, race/ethnicity, marital status,
35 PIR, alcohol intake, smoking status, physical activity, BMI, HTN, DM, HbA1c, TC,
36 and HDL cholesterol between the different AC groups (*P* <0.05).
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42 In addition to that, among those aged 20 years or older (n=30,441), 3,891 (9.79%)
43 participants had missing AC values. The proportion of missing values for the different
44 age groups is shown in Table S2. Fewer proportions of people between 40 and 69
45 years old had missing AC values compared to those under 40 and those over 70 years.
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50 We conducted a threshold saturation effect analysis on the data, and the results
51 suggested a linear correlation between AC and depression (log-likelihood ratio
52 (LLR)=0.051). The results of the threshold saturation effect are displayed in Table S3.
53 Covariance is generally indicated if the tolerance (Tol) is less than 0.1 or the variance
54 inflation factor (VIF) is greater than 10. Therefore, our results can initially ignore the
55 problem of multicollinearity (Table S4).
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Participants in the lowest AC in Q1 (< 1.9310) were likely to be female, younger, more educated, married or cohabitating, non-Hispanic White, wealthier, less physically active, smoked less, consumed more alcohol, had no DM or HTN, higher HDL cholesterol levels, lower BMI, lower HbA1c levels, and TC levels.

In contrast, participants with the highest AC in Q4 (>3.6430) were likely to be male, middle-aged, more highly educated, non-Hispanic White, married or cohabitating, wealthier, consumed less alcohol, never smoked, inactive and obese, had HTN, lower HDL cholesterol levels, higher BMI, higher HbA1c and TC levels.

Table 1. Characteristics of the study population, using National Health and Nutrition Examination Survey data from 2005–2018 (N = 32,502), Weighted

Characteristic	Overall	Atherogenic coefficient quartiles†				p-value
		Q1 (< 1.9310)	Q2 (1.9310 to < 2.6695)	Q3 (2.6695 to < 3.6430)	Q4 (≥ 3.6430)	
Sex (%)						<0.001
Male	48.78 (48.21,49.35)	32.75 (31.33, 34.21)	42.40 (40.95, 43.87)	54.04 (52.56,55.52)	66.36 (65.00,67.70)	
Female	51.22 (50.65, 51.79)	67.25 (65.79, 68.67)	57.60 (56.13, 59.05)	45.96 (44.48, 47.44)	33.64 (32.30, 35.00)	
Age (%)						<0.001
20 to < 40	35.93 (34.76, 37.12)	40.78 (38.93, 42.66)	36.40 (34.73, 38.10)	33.15 (31.58, 34.76)	33.30 (31.69, 34.95)	
40 to <60	37.75 (36.83, 38.67)	29.54 (27.96, 31.18)	35.21 (33.59, 36.87)	40.86 (39.37,42.37)	45.58 (43.89, 47.29)	
≥60	26.32 (25.26,27.40)	29.67 (28.04, 31.36)	28.39 (26.74, 30.09)	25.99 (24.53, 27.50)	21.12 (19.78,22.52)	
Educational level (%)						<0.001
<High school	15.44 (14.36, 16.58)	12.40 (11.24, 13.65)	14.04 (12.70, 15.49)	16.18 (14.78, 17.67)	19.24 (17.90, 20.65)	
Completed high school	23.30 (22.35, 24.27)	20.49 (19.12, 21.93)	22.16 (20.82, 23.56)	24.87 (23.59,26.20)	25.75 (24.17, 27.40)	
>High school	61.26 (59.57, 62.92)	67.11 (65.08, 69.08)	63.80 (61.69, 65.86)	58.95 (56.99, 60.89)	55.02 (52.92, 57.09)	
Race/ethnicity (%)						<0.001
Non-Hispanic White	68.41 (65.86, 70.86)	69.02 (66.42, 71.51)	68.41 (65.87, 70.84)	68.23 (65.19, 71.72)	67.98 (65.01, 70.81)	
Non-Hispanic Black	10.50 (9.27,11.88)	13.76 (12.07, 15.64)	11.32 (9.98, 12.81)	9.65 (8.42, 11.03)	7.20 (6.22, 8.32)	
Mexican American	8.46 (7.22, 9.89)	6.06 (5.10, 7.18)	7.53 (6.34, 8.93)	9.50 (8.04, 11.20)	10.82 (9.06, 12.86)	
Other Hispanic	5.44 (4.65,6.35)	4.27 (3.54, 5.13)	5.22 (4.40, 6.18)	5.83 (4.87, 6.97)	6.47 (5.42, 7.70)	
Other races/multiple races	7.18 (6.50, 7.93)	6.89 (6.08, 7.81)	7.52 (6.63, 8.51)	6.79 (5.96, 7.73)	7.54 (6.67, 8.50)	
Marital status (%)						<0.001
Married/Living with a partner	64.04 (62.84, 65.22)	59.25 (57.29, 61.17)	62.92 (61.31, 64.54)	66.06 (64.48, 67.61)	68.04 (66.58,69.46)	
Widowed/Divorced/Sepa	35.96 (34.78, 37.16)	40.75 (38.83, 42.71)	37.08 (35.49, 38.69)	33.94 (32.39, 35.52)	31.96 (30.54, 33.42)	

rated/Never married								
PIR (%)								<0.001
< 1.00	13.58 (12.64, 14.57)	12.69 (11.51, 13.97)	13.36 (12.18, 14.64)	12.77 (11.70, 13.92)	15.51 (14.13, 17.00)			
1.00 to <2.00	20.31 (19.33, 21.32)	18.88 (17.52, 20.31)	19.48 (18.36, 20.65)	21.07 (19.63, 22.60)	21.83 (20.18, 23.57)			
≥2.00	66.12 (64.45, 67.74)	68.44 (66.44, 70.37)	67.16 (65.18, 69.08)	66.15 (64.30, 67.96)	62.66 (60.14, 65.12)			
Alcohol intake (g/day)	9.38 (8.90,9.87)	12.33 (11.43, 13.24)	8.91 (8.22, 9.61)	7.84 (7.19, 8.49)	8.43 (7.62, 9.25)			<0.001
Smoking status (%)								<0.001
Non-smoker	54.76 (53.63, 55.88)	58.23 (56.66, 59.78)	56.97 (55.26, 58.66)	54.94 (53.42, 56.45)	48.79 (47.25, 50.33)			
Former smoker	25.13 (24.28, 26.00)	24.55 (23.30, 25.85)	24.60 (23.23, 26.02)	26.12 (24.65, 27.66)	25.26 (24.00, 26.56)			
Current smoker	20.11 (19.24, 21.01)	17.22 (16.03, 18.48)	18.44 (17.19, 19.75)	18.94 (17.85, 20.08)	25.95 (24.45,27.51)			
Physical activity (%)								<0.001
Inactive	45.81 (44.18, 47.45)	39.32 (36.97, 41.72)	44.08 (41.77, 46.42)	47.93 (46.10, 49.77)	52.15 (50.11, 54.17)			
Moderate	28.01 (26.94, 29.11)	27.48 (25.78, 29.25)	28.01 (26.30, 29.78)	29.11 (27.52, 30.76)	27.43 (25.81, 29.11)			
Vigorous	8.05 (7.55, 8.59)	8.86 (7.84, 9.99)	8.74 (7.74, 9.85)	7.25 (6.40, 8.20)	7.36 (6.37, 8.48)			
Both moderate and vigorous	18.13 (116.98, 19.34)	24.34 (22.46, 26.33)	19.17 (17.54, 20.93)	15.71 (4.27, 17.25)	13.07 (11.83, 14.42)			
BMI (kg/m ²)	29.10 (28.94,29.26)	26.12 (25.94, 26.30)	28.70 (28.49, 28.90)	30.28 (30.04, 30.52)	31.38 (31.17, 31.59)			<0.001
HTN (%)	38.20 (37.15, 39.25)	32.90 (31.30, 34.54)	36.35 (34.76, 37.96)	40.33 (38.70, 41.98)	43.34 (41.78, 44.93)			<0.001
DM (%)	14.38 (13.77, 15.02)	11.47 (10.59, 12.40)	13.43 (12.48, 14.45)	14.90 (13.73, 16.15)	17.76 (16.69, 18.88)			<0.001
CVD (%)	8.73 (8.25, 9.22)	9.42 (8.55, 10.37)	8.75 (7.97, 9.60)	8.44 (7.65, 9.30)	8.28 (7.45, 9.20)			0.207
Depression (%)	7.69 (7.24, 8.17)	6.48 (5.77, 7.26)	7.16 (6.30, 8.12)	8.27 (7.46, 9.16)	8.89 (8.16, 9.68)			<0.001
HbA1c (%)	5.61 (5.60, 5.63)	5.44 (5.42, 5.47)	5.55 (5.53, 5.57)	5.64 (5.61, 5.67)	5.82 (5.79, 5.86)			<0.001
TC(mmol/L)	5.02 (5.00,5.05)	4.46 (4.43, 4.50)	4.77 (4.74, 4.80)	5.10 (5.07, 5.13)	5.77 (5.73, 5.80)			<0.001
HDL cholesterol (mmol/L)	1.38 (1.37, 1.39)	1.82 (1.80, 1.84)	1.45 (1.44, 1.46)	1.24 (1.24, 1.25)	1.01 (1.00,1.02)			<0.001
Antidepressants (%)	13.17 (12.52, 13.84)	12.65 (11.66, 13.70)	13.76 (12.67, 14.93)	13.25 (12.25, 14.33)	13.01 (11.83, 14.28)			0.477
Anxiolytics, sedatives, and hypnotics (%)	6.78 (6.33, 7.27)	7.29 (6.54, 8.12)	6.78 (6.07, 7.56)	6.31 (5.56, 7.15)	6.75 (5.93, 7.68)			0.339

For continuous variables: survey-weighted mean (95% CI), the *p*-value was by survey-weighted linear regression (svyglm). For categorical variables: survey-weighted percentage (95% CI), the *p*-value was by survey-weighted Chi-square test (svytable).

Abbreviations: DM, diabetes mellitus; CVD: cardiovascular disease; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; HDL, high-density lipoprotein; HTN, hypertension; PIR, poverty-income ratio (ratio of family income to poverty threshold); SD, standard deviation

Association between AC and depression

In the fully adjusted model, we observed a linear relationship between AC and depression (Figure 2). The results of the weighted multivariate logistic regression analysis are presented in Table 2. AC was positively correlated with depression in the crude model (odds ratio [OR]= 1.08, 95% confidence interval [CI]:1.06-1.11, *P* <0.001). A significant association between AC and depression was detected in

Models 1-3 after adjusting for confounders. In Model 3, all variables were adjusted; for every 1 unit increase in AC, the incidence of depression increased by 3% (OR = 1.03, 95% CI = 1.00–1.06, $P = 0.039$).

Table 2. Associations of the atherogenic coefficient with depression (n = 32,502), Weighted.

	Crude Modela		Model 1b		Model 2c		Model 3d	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Per 1 increase	1.08 (1.06,1.11)	<0.001	1.13 (1.10,1.16)	<0.001	1.07 (1.04,1.10)	<0.001	1.03 (1.00,1.06)	0.039
Quartiles								
Q1 (AC: < 1.9310)	Reference [1]		Reference [1]		Reference [1]		Reference [1]	
Q2 (AC: 1.9310 to < 2.6695)	1.11 (0.96,1.30)	0.166	1.18 (1.01,1.38)	0.040	1.07 (0.91,1.25)	0.431	1.04 (0.89,1.22)	0.589
Q3 (AC: 2.6695 to < 3.6430)	1.30 (1.11,1.53)	0.001	1.48 (1.26,1.74)	<0.001	1.24 (1.07,1.45)	0.006	1.18 (1.02,1.38)	0.034
Q4 (AC: ≥ 3.6430)	1.41 (1.22,1.62)	<0.001	1.75 (1.50,2.03)	<0.001	1.32 (1.14,1.54)	<0.001	1.15 (0.99,1.33)	0.074
<i>p</i> for trend	<0.001		<0.001		<0.001		0.040	

Abbreviations: AC, atherogenic coefficient.

aModel 1: Adjusted for age, sex, and race/ethnicity.

bModel 2: Adjusted for the variables in Model 1 plus body mass index, poverty-income ratio, educational level, and marital status.

cModel 3: Adjusted for the variables in Model 2 plus hypertension, diabetes mellitus, alcohol intake, smoking status, physical activity, and glycosylated hemoglobin.

After adjusting for age, sex, race/ethnicity, BMI, PIR, educational level, marital status, HTN, DM, alcohol intake, smoking status, physical activity, and HbA1c compared with participants in the first quartile (AC < 1.9310), the second group (1.9310 to < 2.6695, OR = 1.04, 95% CI = 0.89– 1.22, $P = 0.589$), the third group (2.6695 to < 3.6430, OR = 1.18, 95% CI = 1.02– 1.38, $P = 0.034$), and the fourth group (≥ 3.6430 , OR = 1.15, 95% CI = 0.99– 1.33, $P = 0.074$) had an increased prevalence of depression (P for trend was significant in all the models).

Furthermore, regarding the interaction between sex and the relationship between AC and depression, the relationship was more significant in females (OR = 1.07, 95% CI = 1.02–1.12, *P* for interaction = 0.027) (Table 3).

Table 3. Subgroup analysis of the effect of the atherogenic coefficient on depression (n = 32502), Weight.

Subgroup	Number of participants	OR (95% CI)	<i>P</i> for interaction
Sex, n (%)			0.027
Male	15954	1.05 (1.01, 1.10)	
Female	16548	1.07 (1.02, 1.12)	
Age, n (%)			0.375
20 – < 40	10857	1.07 (1.02, 1.12)	
40 – < 60	10632	1.04 (0.99, 1.09)	
≥ 60	11013	1.04 (0.97, 1.11)	
Race/ethnicity, n (%)			0.196
Non-Hispanic White	14112	1.03 (0.99, 1.08)	
Non-Hispanic Black	6713	1.06 (0.98, 1.15)	
Mexican American	5174	1.05 (0.97, 1.14)	
Other Hispanic	3109	1.12 (1.06, 1.19)	
Other race/multiple races	3394	1.10 (0.96, 1.26)	
BMI, kg/m ² , mean (SD)			0.212
Low	10729	1.08 (1.00, 1.17)	
Middle	10733	1.06 (1.01, 1.12)	
High	10743	1.03 (0.99, 1.08)	
Hypertension, n (%)			0.949
Yes	13940	1.04 (1.00, 1.08)	
No	18562	1.06 (1.01, 1.12)	
DM, n (%)			0.670
Yes	6152	1.03 (0.98, 1.08)	
No	25761	1.07 (1.03, 1.11)	

Abbreviations: BMI, body mass index (calculated as weight, in kilograms, divided by the square of height, in meters); DM, diabetes mellitus; HTN, hypertension

DISCUSSION

This cross-sectional study showed an association between AC and depression in adults in the United States. After adjusting for covariates, a positive linear relationship was found between AC and depression.

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4 The details of the mechanism explaining the relationship between AC and
5 depression need to be further explored, and there may be several possible
6 explanations. Lipids and the immune system interact with one another and have a
7 regulatory effect on each other. Dysregulated inflammation promotes susceptibility to
8 depression [23]. Studies have shown that inflammatory cytokines produced in the
9 periphery enter the cells of the central nervous system and can affect
10 neurotransmitters and neural circuits, producing behavioral symptoms of depression
11 [24]. When T lymphocytes are activated, they not only participate in immune
12 inflammation but also directly contribute to the development of depression when
13 functionally impaired [25,26]. Lipid peroxidation and oxidation-specific epitopes are
14 formed, and the levels of antioxidants such as glutathione, glutathione peroxidase, and
15 coenzyme Q10 are reduced, resulting in or aggravating oxidative stress [27,28].

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When lipids are abnormal, the inflammatory, oxidative, and nitrosative (IO&NS) pathway is further activated [29]. At this time, the increase in binding globin and high-sensitivity C-reactive protein (CRP) is accompanied by a significant increase in interleukin-6 (IL-6), tumor necrosis factor- α , interferon- γ , other pro-inflammatory cytokines, and immune inflammation [30]. These factors lead to defects in serotonin and melatonin through the kynurenine pathway, often considered one of the main causes of depression [31]. Activation of the IO&NS pathway leads to mitochondrial and subsequent cellular dysfunction [32]. Previous studies have linked mitochondrial dysfunction in various brain regions to depression [33].

Statins have also been shown to have antidepressant effects when co-prescribed with antidepressants [34]. Lowering the AC index of patients with mood disorders improves CVD outcomes [35]. CVD is a heart and blood vessel disease characterized by myocardial infarction, angina pectoris, heart failure, heart attack, and stroke [36]. Longer exposure to depression is associated with significantly increased CVD risk [37]. Factors contributing to the link between depression and cardiac outcome may include alterations in the autonomic nervous system, platelet receptors and function, coagulopathic factors, pro-inflammatory cytokines, endothelial function, neurohormonal factors, and genetic linkages [38]. At the same

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4 time, patient compliance with antidepressant treatment is relatively poor [39].
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6 Atherosclerosis is a chronic vascular inflammatory disease associated with oxidative
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8 stress and endothelial dysfunction [40]. Atherosclerosis is the underlying cause of
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10 CVD, and AC is a major indicator of atherosclerosis [41]. Our results suggest that AC
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12 may play a role in depression. AC may indicate the relationship between CVD and
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14 depression and a potential target and marker for treating depression or depression
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16 combined with CVD. The relevant mechanisms remain to be explored further.

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18 Our study found increased odds of depression with increased AC in adults,
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20 demonstrating that controlling AC may be beneficial for preventing depression. Sex
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22 may affect this relationship. In the subgroup analysis (Table 3), we found a stronger
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24 relationship between AC and depression in females. The synergistic effect of estrogen
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26 on cognitive and emotional functions may underlie the association between ovarian
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28 hormone fluctuations and depression in females [42]. The induction of indoleamine 2,
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30 3-dioxygenase, and deleterious effects of tryptophan catabolizing metabolites
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32 (TRYCATs) play a role in the pathophysiology of depression. Activation of IDO
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34 decreases plasma tryptophan levels and increases TRYCAT synthesis in depressed
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36 individuals. Females showed more IDO activation and TRYCAT production after
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38 immune challenge than males [43]. Therefore, this sex difference in immune
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40 dysregulation may contribute to higher levels of anxiety and depression experienced
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42 by females.

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44 This study has some limitations. First, this was a cross-sectional study;
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46 therefore, we could not determine a causal relationship between AC and depression.
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48 Second, the PHQ-9 is a proven, simple, and effective tool for identifying the severity
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50 of depressive symptoms, but it is not a diagnostic tool for MDD. Third, the
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52 relationship we studied may have been influenced by other confounding factors,
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54 which we have not adjusted. Fourth, the differences in demographics and population
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56 characteristics in the United States may limit the generalizability of the findings to
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58 other countries or regions. Fifth, AC is associated with both depression and CVD,
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60 which may potentially affect the nervous system and mental health. At the same time,
there are also uncontrollable variables such as lifestyle and regional culture. Finally,

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4 although collinearity statistics did not find any significant collinearity, relationships
5 that are beyond statistical p -values may exist.
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9 **CONCLUSIONS**

10 Our research shows that higher AC levels in American adults are positively related to
11 a higher prevalence of depression. Further studies are required to explore the
12 underlying mechanisms and potential benefits of controlling AC levels in patients
13 with depression.
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29 J Yin; validation, H Sun, Y Liu and J Yang; formal analysis, L Zhang, J Yin, and H Sun;
30 investigation, L Zhang; resources, L Zhang; data curation, H Sun; writing—original draft
31 preparation, L Zhang; writing—review and editing, Y Liu and J Yang; visualization, J Yin;
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46 **Data Sharing Statement:** The original contributions presented in the study are included in
47 the article/supplementary material, further inquiries can be directed to the corresponding
48 author.
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51 **Ethics Statement:** The National Center for Health Statistics (NCHS) Research Ethics Review
52 Board (ERB) authorized the NHANES study protocols. The data for this study were obtained
53 from the NHANES database, no one was directly involved, and no additional ethical
54 guidelines were required.
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25 26 27 28 29 30 31 32 33 34 35 **FIGURE LEGENDS**

36
37 **Figure 1.** Flowchart for inclusion of study participants.

38
39 **Figure 2.** Association between AC and depression in US adults (n=4759). The black
40 vertical line on the horizontal axis represents the AC distribution, the red line
41 represents the best fit, and the difference between the dashed lines represents the 95%
42 confidence interval. The data was adjusted for age, sex, race/ethnicity, body mass
43 index, poverty-income ratio, educational level, marital status, hypertension, diabetes
44 mellitus, alcohol intake, smoking status, physical activity, and glycosylated
45 hemoglobin.
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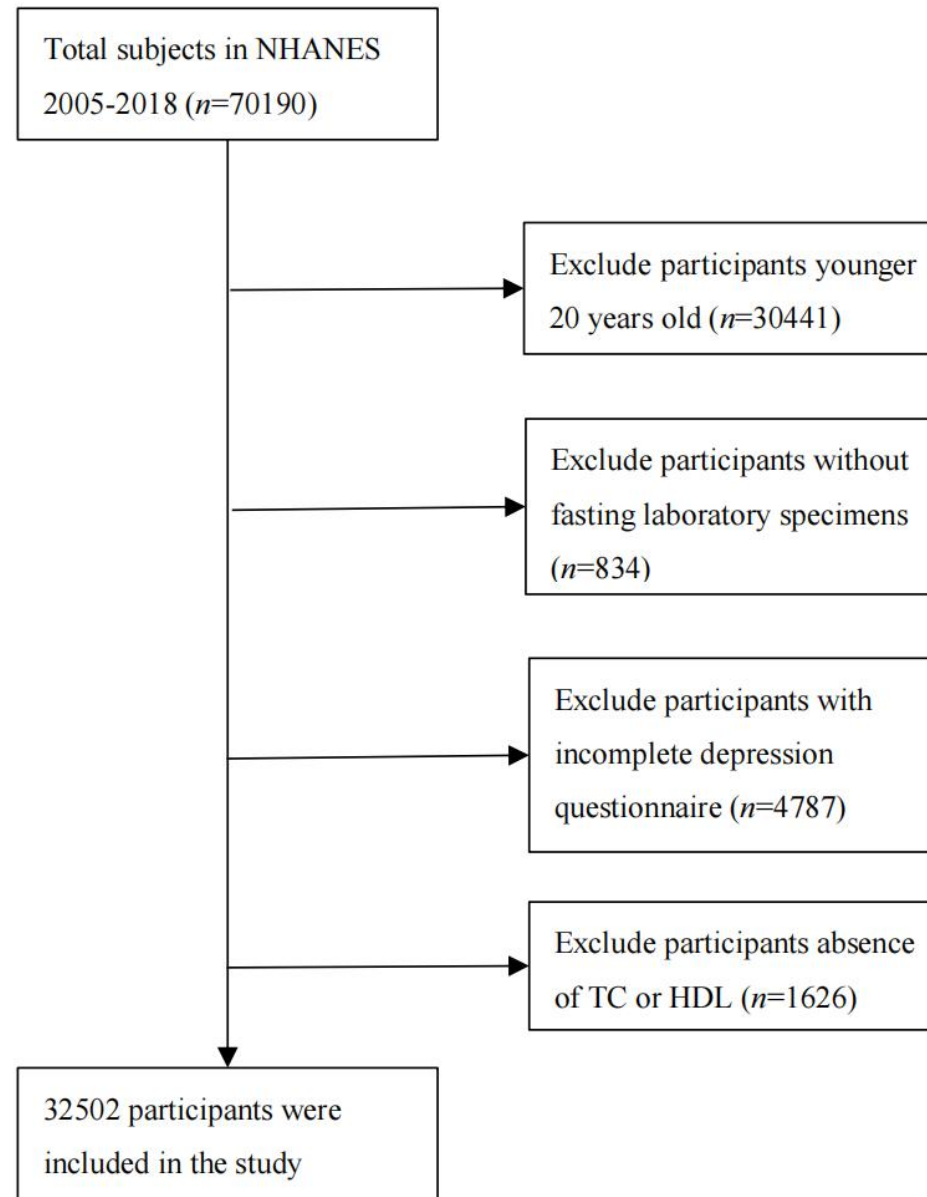


Figure 1. Flowchart for inclusion of study participants.

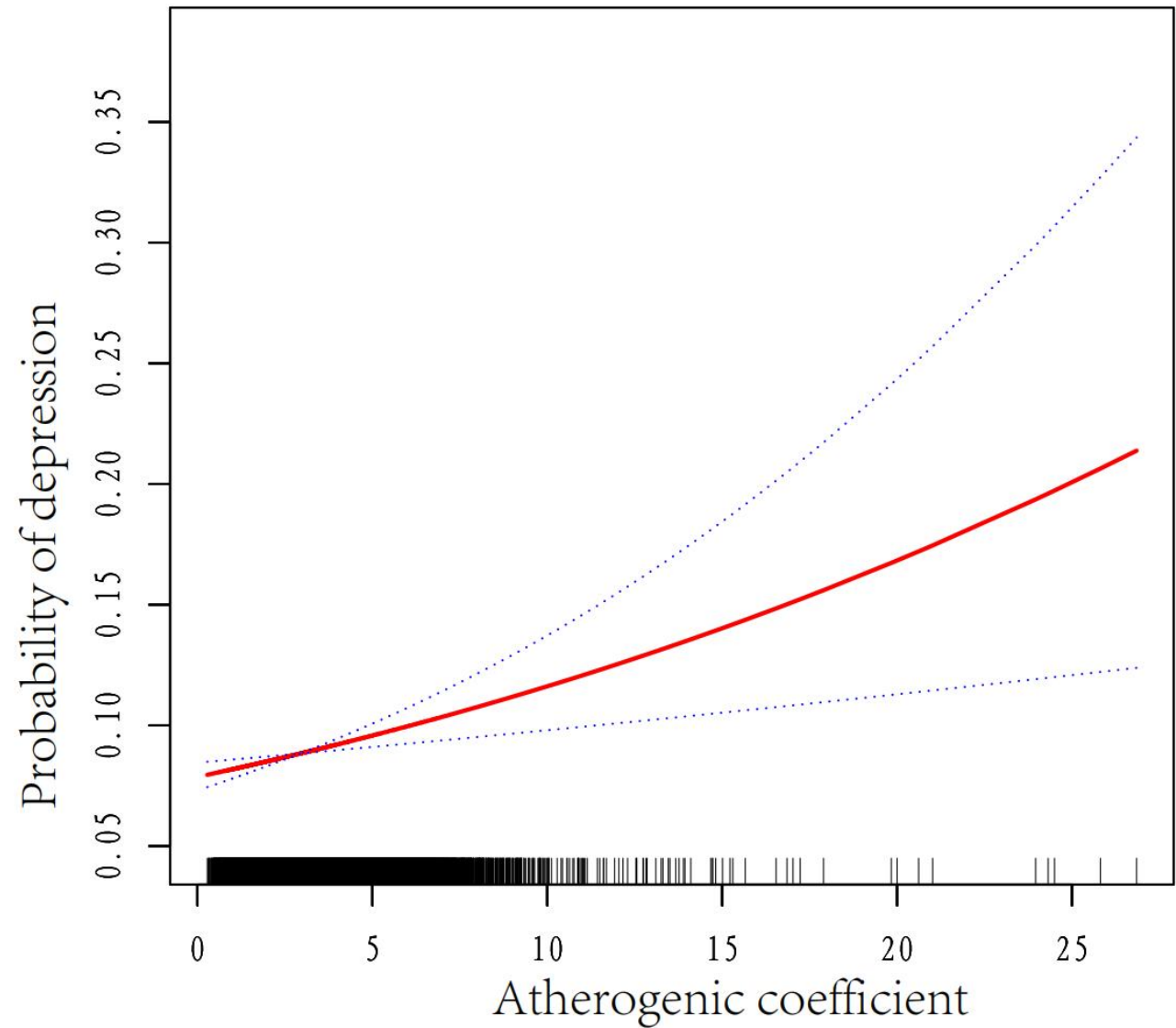


Table S1. Missing covariates of study participants (n = 32502)

Variable	Number of patients (% missing)
Age	0 (0%)
Sex	0 (0%)
Race/ethnicity	0 (0%)
Educational level	23 (0.07%)
Marital status	16 (0.04%)
Poverty-income ratio	2767 (8.51%)
Body mass index	297 (0.91%)
Alcohol intake	4661 (14.34%)
Smoking status	17 (0.05%)
Physical activity	4102 (12.62%)
Hypertension	0 (0%)
Diabetes mellitus	589 (1.81%)
Glycosylated hemoglobin	58 (0.18%)

Table S2. Absence of atherogenic coefficient in adults

Age (y)	Missing number (n)	Total number (n)	Proportion (%)
20-29	729	6029	12.09
30-39	665	6044	11.00
40-49	527	6060	8.70
50-59	524	5691	9.21
60-69	575	5974	9.63
70-79	425	3730	11.39
≥80	446	2330	19.14

Table S3. Threshold effect analysis for association of atherogenic coefficient with depression

Outcomes	Depression	P-value
Model 1, β (95%)		
Linear effort model	1.04(1.02,1.07)	0.002
Model 2, β (95%)		
Infection point (K)	1.2	
K <1.2	0.54 (0.29,1.03)	0.059
1.2 >K	1.05 (1.02,1.08)	<0.001
LLR	0.051	

Table S4. Results of collinearity detection

Mode		Unstandardized		Standardized	t	Significance	Collinearity	
		Coefficients					Statistics	
1		B	Standard Error				Tolerance	VIF
1	Constant	-0.067	0.01		-6.668	0		
	AC	0.002	0.002	0.01	1.089	0.276	0.153	6.524
	HDL	-0.002	0.006	-0.003	-0.349	0.727	0.193	5.177
	cholesterol							
	TC	-0.001	0.002	-0.002	-0.312	0.755	0.269	3.723
	HbA1c	0.001	0.001	0.004	0.973	0.33	0.936	1.068

Dependent Variable: Depression.

Abbreviations: AC, atherogenic coefficient; HDL, high-density lipoprotein; TC, total cholesterol; HbA1c, glycosylated hemoglobin.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	4
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.