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TOTAL SERUM CHOLESTEROL AND DEPRESSION IN ADULTS: ASSOCIATION AND PUBLIC

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Abstract

Objective:
This objective of this study is to conduct a thorough and updated analysis on the relationship between cholesterol and depression for more consistency in the literature, and allowing for healthcare professionals to collaborate with each other in order to provide appropriate interventions for the general public.

Methods:
The 2017-2018 NHANES survey was utilized to conduct a cross-sectional analysis on the association between cholesterol and depression. The sample size for this study was narrowed down to 5,097 survey participants. Univariate, bivariate, stratified, and multivariate analyses were conducted in order to fully assess the relationship between cholesterol and depression.

Results:
Body mass index and diet both interact with high cholesterol, increasing the odds of depression [(OR: 1.16, 90% CI: 1.03 – 1.31; OR: 1.50, 90% CI: 1.15 – 1.96), respectively]. An interaction exists between diet and low cholesterol, also increasing the odds of depression (OR: 1.44, 90% CI: 1.01 – 2.07).

Conclusion:
While the crude association between cholesterol and depression show a protective effect, body mass index and diet interact with high and low cholesterol, producing an increase in the odds of depression. Future research and policy showed focus more on developing healthcare professional awareness and collaboration in order to provide immediate, appropriate, and effective interventions for this association.

Introduction

In the U.S. alone, 38% of adults have high cholesterol (Virani, et. al, 2020). Because it is silent in nature and has no presenting symptoms, high cholesterol has been deemed a silent killer as it raises the risk for heart disease and stroke, both major leading causes of mortality (CDC, 2020). While high cholesterol is often discussed as a major risk factor for morbidity and mortality, low cholesterol is sometimes neglected as a risk factor for morbidity and mortality as well. Previous studies have shown inconsistent results between low cholesterol and morbidity and mortality, yet others have found an association overall, where low cholesterol can have as much as a 30% increase in disease and mortality (Jeong, et. al, 2019).

As mental health advocacy, screening, and treatment has become increasingly more popular over the last decade, the prevalence of depression has been increasing as well. Depression has become one of the most prevalent mental illnesses in the United States, causing massive impairments in human functionality, and can even result in death (Machado, et. al, 2018). In 2017, among those aged 18 or older, over 17 million U.S. adults have experienced at least one major depressive episode, defined in the DSM-5 as having a depressed mood or loss of interest in daily activities with several other debilitating symptoms for a period of a least two weeks. Various studies have suggested that the prevalence of depression is higher amongst younger adults (U.S. DHHS, 2019), whereas others have revealed a higher prevalence in older adults (Luppa, et. al, 2012). Depression is more prevalent in females than males (U.S. DHHS

2019), those who are white, those with low income (Riolo, et. al, 2019), and has been becoming more prevalent among immigrants residing in the United States for 15 years or more (Ikonte, et. al, 2020). With the ongoing COVID-19 pandemic, the prevalence of depression and depressive-like symptoms in the United States is 3 times greater than it was before the pandemic (Gradus, 2020).

While there are evident threats behind high cholesterol, low cholesterol, and depression – interventions do exist to mediate these conditions. For high cholesterol or hyperlipidemia, influence may stem from genetics, weight, BMI, smoking, lack of exercise, or poor diet. Thus, key interventions that commonly lower cholesterol include prescription medication, low-fat diet, exercise, cessation of smoking, and/or lowering weight (American Heart Association, 2020). For low cholesterol or hypolipidemia, influence may come from genetic or secondary causes, such as hypothyroidism, chronic infections, cancers, chronic alcohol use, and malabsorption. Thus, key interventions to raise cholesterol include dietary fat and fat-soluble vitamin supplementation (Davidson, 2019). For depression, most adults choose to intervene with a qualified health professional such a psychologist or licensed therapist in combination with prescription medication. However, 35% of U.S. adults receive no form of treatment for depression (U.S. DHHS, 2019).

The relationship between cholesterol and mental health is inconsistent and with numerous outdated studies. In a study of Japanese male workers, high serum cholesterol was associated with depression, where a higher prevalence of major depression was seen amongst Japanese men with high cholesterol (Nakao & Yano, 2004). However, another study of Croatian war veterans showed that higher cholesterol had a protective effect against the odds of depression (Vilibić, 2014). On the other hand, other studies have suggested that low serum cholesterol is associated with depression (Morgan, et. al, 1993), and even suggested a U-shape association between low to high cholesterol and depression (Tedders, et. al, 2011). Furthermore, studies have suggested an association between low cholesterol and depression amongst middle-aged men (Steegman, et. al, 2000) and the elderly (Manfredini, et. al, 2000). One study has even indicated that there is no association at all between cholesterol and depression, and cholesterol in general cannot serve as a suitable biological marker for depression screening (Deisenhammer, et. al, 2004).

Cholesterol and depression have become the two leading components of death amongst adults in the United States. With millions of adults in the U.S. already at increased risk of poor health due to their cholesterol levels or state of depression, it is imperative to understand the association between the two in order to address the necessary interventions that can work simultaneously to prevent premature morbidity and mortality.

This objective of this study is to provide an updated analysis in the relationship between cholesterol and depression, and to allow for more consistency with the literature on this association. Additionally, it will allow for physicians to intervene with at-risk patients and refer them to the appropriate mental health providers and interventions when necessary. This study will also educate a regular person to be more cognizant of their cholesterol levels in relation to their mental health, thus allowing for immediate action in seeking out mental healthcare or other interventions in a preventative fashion.

Methods

Study Design

This study implements a cross-sectional study design in order to assess the association between high cholesterol and depression, as well as low cholesterol and depression. In order to allow for more sensitivity in the definition of depression, this study did not restrict depression to major depressive disorder. This study also utilized an objective measurement of cholesterol in order to allow for a more accurate analysis of the association between cholesterol and depression.

Data Source

This study used the 2017-2018 National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention (CDC). NHANES is comprised of various physical and mental health assessments in the form of interviews, exams, and laboratory testing. Through these assessments on demographics, dietary, and a multitude of health-related topics, NHANES serves to highlight and monitor trends in health, disease, and risk factors for that survey cycle year. The 2017-2018 NHANES dataset selected 16,211 people to participate in the cycle, upon which 9,254 completed the interview and 8.704 participated in examinations.

Primary Outcome

The primary health outcome of this study was depression. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines a major depressive episode as having a depressed mood or loss of interest in daily activities with issues in sleep, eating, energy, and concentration for a period of a least two weeks (U.S. DHHS, 2019). For the purpose of this study, depression was not restricted to major depressive disorder. NHANES participants were asked “How often do you feel depressed? Would you say daily, weekly, monthly, a few times a year, or never?” Those who responded “never” were categorized as “no depression”, whereas those who answered anything ranging from “daily” to “a few times a year” were categorized as “depressed.” This primary outcome was coded as a binary categorical variable.

Primary Exposures

The primary exposure of this study was cholesterol. In order to fully understand the association between high cholesterol and depression, as well as low cholesterol and depression, the cholesterol variable was coded and categorized into two separate binary cholesterol variables: high cholesterol and low cholesterol. NHANES provided an objective measurement of cholesterol in mg/dL through the laboratory testing portion of the survey. For the high cholesterol variable, those with total serum cholesterol greater than 200 mg/dL were classified as having high cholesterol, and anything greater than 158 mg/dL and less than or equal to 200 mg/dL was classified as normal cholesterol. 158 mg/dL was used as the cutoff between normal cholesterol and low cholesterol, as the 1st quartile of the study sample has a cholesterol level of

158 mg/dL or less. With the same logic, for the low cholesterol variable, those with a total cholesterol level greater than 158 mg/dL and less than or equal to 200 mg/dL was classified as normal cholesterol, and those with measurement of 158 mg/dL were classified as low cholesterol. These two primary exposures are binary categorical variables.

Potential Confounders and Effect Modifiers

This study implemented an analysis on potential confounders and effect modifiers in the relationship between the primary exposures and outcome. The other variables that were assessed included sex, age, household income, level of education, alcohol use, smoking status, body mass index, moderate exercise, diet, aspirin, and numerous health conditions commonly associated with high and low cholesterol. These health conditions include: hypertension, congestive heart failure, coronary heart disease, angina, myocardial infarction, stroke, thyroid issues, liver disease, and cancer.

Covariate descriptions:

Sex – Participants' sex (male or female).

Age – Age of participants in years, and restricted to adults aged 18 year and older. Age was categorized into three categorical groups: young adults (18 – 34), adults (35-65) , and older adults (65 and older).
Household income – the combined income of all members of the same household of the participant. Household income was categorized into four categorical levels based on the mean and upper limit cutoffs from 2018 U.S. census data.

Level of education – the highest level of education completed by participants, categorized into 5 levels: less than 9^{th} grade, did not complete high school, high school diploma or GED equivalent, some college or associates degrees, and college degree or above.

Alcohol use – the frequency of any alcohol usage by the participants in the past 12 months, categorized as: daily, weekly, monthly, a few times a year, or never.

Smoking status – the smoking status of participants, restricted to cigarette use only, and categorized into 3 levels: current smoker (has smoked over 100 cigarettes in their lifetime and currently smokes), former smoker (has smoked over 100 cigarettes in their lifetime and does not currently smoke), and never (has neither smoked over 100 cigarettes in their life nor currently smokes).

Body mass index – the ratio of weight to height of the participants in units of kg/m^2, and categorized into 4 levels: underweight (less than 18.5 kg/m^2), normal (between 18.5 and 24.9 kg/m^2), overweight (between 25.0 and 30.0 kg/m^2), and obese (over 30.0 kg/m^2).

Moderate exercise – moderate exercise status of the participants, defined as having at least 10 consecutive minutes in a day of moderate recreational activity with an increase in heart rate and/or breathing, categorized as a binary variable: frequent (greater than or equal to 3 days of moderate exercise per week) and non-frequent (0 to 3 days of moderate exercise per week).

Diet – current diet status of the participants, defined as currently being on a special diet for health or weight-loss purposes, categorized as a binary variable: yes (on a special diet) and no (not on any diet).

Aspirin – current status of aspirin medication of the participant, defined as currently taking aspirin or not taking aspirin at all, and categorized into a binary variable: yes (currently taking aspirin) and no (not taking any aspirin).

Health conditions – defined as participants having been told by a doctor or other health professional that they have one of the following conditions: hypertension, congestive heart failure, coronary heart disease, angina, myocardial infarction, stroke, thyroid issues, liver disease, and cancer. These variables were categorized into binary variables and yes (have been informed by a doctor or other health professional) and no (have not been told by a doctor or health professional).

Comorbidities – defined as having two or more of the defined health conditions above simultaneously. This variable was calculated by summing the number of health conditions reported by each participants, and then calculating it into a score ranging from 0-7. Comorbidities were codes as a binary variable, where yes indicated having two or more of the defined health conditions above simultaneously, and no indicated have less than two health conditions.

Analytic Approach

Statistical analysis was conducting using SAS OnDemand for Academics (SAS Studio Enterprise 3.8) in order to investigate both associations of high cholesterol and depression, as well as low cholesterol and depression. The 2017-2018 NHANES dataset selected 16,211 people to participate in the cycle, upon which 9,254 completed the interview and 8.704 participated in examinations. In this study, the sample size was narrowed down to those above 18 years of age, and had completed both exposure and outcome variables. As a result, the sample size resulted in 5,097 participants for this study. Univariate analysis was conducted by calculating the prevalence of main exposures and other covariates in relation to the main outcome variable. Bivariate analysis was conducted by cross-tabulating and creating 2x2 tables of the main exposures, other covariates, and the main outcome variable. Crude odds ratios, 90% confidence intervals, and chi-square p-values were calculated in order to analyze the association between main exposures, other covariates, and the main outcome variable. Variables that were significantly associated with the main outcome variable at $p<0.10$ were further assessed in a stratified analysis between the main exposures and outcome variable in order to assess for

potential confounders and effect modifiers. Stratum-specific odds ratios were calculated and compared to the crude odds ratio between the main exposures and outcome variable. Each variable was assessed for homogeneity using the Breslow Day Test of Homogeneity, and stratum specific odds ratios were adjusted for using the Cochran-Mantel-Haenzel test. Differences between adjusted odds ratios and the crude odds ratio of exposures and outcome variables were compared in order to classify confounders and effect modifiers. Multivariate logistic regression models were created in order to analyze the relationship between statistically significant predictors and the main outcome variable, accounting for potential confounders and effect modifiers. Model selection was applied using backwards selection in order to create a more parsimonious multivariate model for the true association between the predictors and main outcome variable.

Results

Table 1. Univariate and Bivariate Analysis

	N (%)	Depression (%)	No Depression (%)	Crude OR	90% CI
Total	5097 (100)	2710 (53.2)	2387 (46.8)	---	---
High Cholesterol (mg/dL)					
High (> 200)	1754 (45.9)	916 (52.2)	838 (47.8)	0.89	(0.80 – 0.99)*
Normal (158 < x ≤ 200)	2068 (54.1)	1136 (54.9)	932 (45.1)	ref	ref
Low Cholesterol					
Low (≤ 158)	1275 (38.1)	658 (51.6)	617 (48.4)	0.87	(0.77 – 0.98)*
Normal (158 < x ≤ 200)	2068 (61.9)	1136 (54.9)	932 (45.1)	ref	ref
Sex					
Male	2450 (48.1)	1169 (47.7)	1281 (52.3)	0.66	(0.59 – 0.73)****
Female	2647 (51.9)	1541 (58.2)	1106 (41.8)	1.53	(1.38 – 1.71)****
Age (years)					
Young adult (18 – 34)	1413 (27.2)	784 (55.5)	629 (44.5)	1.20	(1.05 – 1.37)***
Adult (34 – 65)	1503 (29.5)	814 (54.2)	689 (45.8)	1.14	(1.02 – 1.27)*
Older Adult (>65)	2181 (42.8)	1112 (51.0)	1069 (49.0)	ref	ref
Race/Ethnicity					
White	1787 (35.1)	1024 (57.3)	763 (42.7)	ref	ref
Black	1128 (22.1)	563 (49.9)	565 (50.1)	0.74	(0.64 – 0.86)****
Hispanic	1199 (23.5)	658 (54.9)	541 (45.1)	0.91	(0.80 – 1.02)
Asian	714 (14.01)	301 (42.3)	413 (57.8)	0.54	(0.46 – 0.65)****
Other	269 (5.3)	164 (61.0)	105 (39.0)	1.16	(0.94 – 1.45)
Household Income (USD)`					
Less than $25,000	1198 (25.9)	734 (61.3)	464 (38.7)	2.02	(1.74 – 2.34)****
$25,000 - $55,000	1547 (33.4)	832 (53.8)	715 (46.2)	1.48	(1.29 – 1.71)****
$55,000 - $99,999	1002 (21.6)	505 (50.4)	497 (49.6)	1.30	(1.11 – 1.51)***
$100,000 or more	884 (19.1)	388 (43.9)	496 (56.1)	ref	ref
Education Level					
Less than 9th grade	402 (8.3)	219 (54.5)	183 (45.5	1.32	(1.09 – 1.60)**

Did not finish high school	547 (11.3)	314 (57.4)	233 (42.6)	1.49	(1.25 – 1.76)***
High school grad or GED	1150 (23.7)	616 (53.6)	543 (46.4)	1.27	(1.11 -1.46)***
Some college	1586 (32.7)	879 (55.4)	707 (44.6)	1.37	(1.20 – 1.55)****
College grad or higher	1168 (24.1)	555 (47.5)	613 (52.5)	ref	ref
Alcohol Use					
Daily	278 (6.5)	158 (56.8)	120 (43.2)	1.12	(0.89 – 1.40)
Weekly	881 (20.7)	481 (54.6)	400 (45.4)	1.02	(0.87 – 1.19)
Monthly	911 (21.4)	510 (56.0)	401 (44.0)	1.08	(0.92 – 1.25)
Few times a year	1221 (28.6)	665 (54.5)	556 (45.5)	1.01	(0.88 – 1.17)
Never	973 (22.8)	526 (54.1)	447 (45.9)	ref	ref
Smoking status (cigarettes)					
Current smoker	866 (17.4)	581 (65.6)	305 (34.4)	2.00	(1.75 – 2.28)****
Former smoker	1184 (23.2)	654 (55.2)	530 (44.8)	1.30	(1.15 – 1.45)***
Never Smoked	3027 (50.4)	1475 (48.7)	1552 (51.3)	ref	ref
Body Mass Index (kg/m^2)					
Underweight (<18.5)	81 (1.6)	46 (56.8)	35 (43.2)	1.21	(0.82 – 1.76)
Normal (18.5 – 24.9)	1250 (24.9)	651 (52.1)	599 (47.2)	ref	ref
Overweight (25.0 – 29.9)	1598 (31.8)	765 (47.9)	833 (52.1)	0.84	(0.74 – 0.95)**
Obese (>30.0)	2094 (41.7)	1203 (57.5)	891 (42.5)	1.24	(1.10 – 1.39)***
Exercise (days per week)					
Frequent (> 3)	1406 (68.1)	705 (50.1)	701 (49.9)	0.99	(0.82 – 1.15)
Non-frequent (< 3)	659 (31.9)	332 (50.1)	327 (49.9)	ref	ref
Diet					
Currently on a health diet	756 (16.3)	440 (58.2)	316 (41.8)	1.25	(1.07 – 1.47)***
No diet	3887 (83.7)	2047 (52.7)	1840 (47.3)	ref	ref
Surgery					
Yes	65 (1.3)	38 (58.5)	27 (41.5)	1.23	(0.81 – 1.88)
No	5032 (98.7)	2762 (53.1)	2360 (46.9)	ref	ref
Medication (Aspirin)					
Yes	971 (70.3)	505 (52.0)	466 (48.0)	0.84	(0.69 – 1.03)
No	410 (29.7)	230 (56.1)	180 (43.9)	ref	ref
Health Conditions					
Hypertension	1854 (36.4)	1054 (56.9)	800 (43.1)	1.26	(1.14 – 1.39)****
CHF	171 (3.5)	107 (62.6)	64 (37.4)	1.50	(1.14 – 1.94)**
CHD	227 (4.7)	136 (59.9)	91 (40.1)	1.33	(1.06 – 1.67)**
Angina	140 (2.9)	90 (63.3)	50 (35.7)	1.61	(1.29 – 2.16)***
Myocardial Infarction	236 (4.9)	139 (58.9)	97 (41.1)	1.28	(1.02 – 1.60)*
Stroke	224 (4.6)	142 (63.4)	82 (36.6)	1.55	(1.23 – 1.96)***
Thyroid Issues	591 (12.2)	351 (59.4)	240 (40.6)	1.33	(1.15 – 1.54)***
Liver Disease	263 (5.4)	176 (66.9)	87 (33.1)	1.84	(1.46 – 2.29)****
Cancer	497 (10.2)	274 (55.1)	223 (44.9)	1.09	(0.93 – 1.27)

* $p < 0.1$
** $p < 0.05$
*** $p < 0.01$
**** $p < 0.0001$

The final sample size for this study was 5,097 adults ages 18 and older. Table 1 shows the univariate and bivariate analysis of the association between the mains exposures, covariates, and main outcome variable. The prevalence of depression in the sample size was 53.2%. The odds of having depression among those with high cholesterol was 11% less than those with normal cholesterol (OR: 0.89, 90% CI: 0.80, 0.99). The odds of having depression among those with low cholesterol with 13% less than those with normal cholesterol (OR: 0.89, 90% CI: 0.80, 0.99). Among males, the odds of having depression was reduced by 34% (OR: 0.66, 90% CI: 0.59 0.73), whereas females had a 53% increase in the odds of having depression (OR: 1.53, 90% CI: 1.38, 1.71). The odds of depression was highest in young adults (OR: 1.20, 90% CI: 1.05, 1.37). Blacks saw a 26% reduction in the odds of having depression (OR: 0.74, 90% CI: 0.64, 0.86), although Asians had an even greater protective affect against the odds of having depression (OR: 0.54, 90% CI: 0.46, 0.65). Those a household income of less than $25,000 had a two-fold increase in the odds of having depression (OR: 2.02, 90% CI: 1.74, 2.34). Individuals who reported less than having graduated college showed at least a 27% increase in the odds of having depression. Among smokers, current smokers had a two-fold increase in the odds of having depression (OR: 0.89, 90% CI: 0.80, 0.99), whereas former smokers had a 30% increase in the odds of having depression (OR: 1.30, 90% CI: 1.15, 1.45). Individuals who were obese had a 24% increase in the odds of having depression (OR: 1.24, 90% CI: 1.10, 1.39), however, those who were overweight showed a 16 percent decrease in the odds of having depression (OR: 0.84, 90% CI: 0.74, 0.95). Any individual who reported being on a diet for health or weight loss purposes had a 25% increase in the odds of having depression. Finally, individuals who reported any of the following health conditions showed a minimum of a 26% increase in the odds of having depression: hypertension, CHF, CHD, angina, myocardial infarction, stroke, thyroid issues, or liver disease.

Table 2.1. Stratified analysis of the association between high cholesterol and depression

Variable	Stratum-Specific OR (90% CI)	Breslow Day Test of Homogeneity (p-value)	Adjusted OR (90% CI)
Crude Association	0.89 (0.80 – 0.99)*		
Sex			
Male	0.93 (0.78 – 1.08)	0.5424	0.88 (0.79 – 0.98)*
Female	0.85 (0.73 – 0.98)*		
Age			
Young adult	0.87 (0.68 – 1.09)	0.5085	0.90 (0.81 – 1.01)
Adult	1.00 (0.83 – 1.21)		
Older Adult	0.85 (0.72 – 1.01)		
Race			
White	1.08 (0.90 – 1.30)	0.2745	0.89 (0.80 – 0.99)*
Black	0.80 (0.63 – 1.01)		
Hispanic	0.86 (0.68 – 1.06)		

Asian	0.72 (0.54 – 0.95)*		
Other	0.91 (0.56 – 1.45)		
Household Income			
Less than $25,000	1.07 (0.85 -1.35)	0.2195	0.93 (0.83 – 1.05)
$25,000 - $55,000	1.03 (0.85 -1.25)		
$55,000 - $99,999	0.74 (0.558– 0.94)**		
$100,000 or more	0.87 (0.67 – 1.12)		
Education			
Less than 9th grade	0.95 (0.65 – 1.38)	0.6319	0.89 (0.79 – 0.99)
Did not finish high school	0.97 (0.69 – 1.36)		
High school grad or GED	0.80 (0.64 – 1.01)		
Some college	1.00 (0.82 – 1.21)		
College grad or higher	0.79 (0.63 – 0.98)*		
Body Mass Index			
Underweight	1.37 (0.45 – 4.13)	0.0502	0.90 (0.81 – 1.01)
Normal	0.81 (0.64 – 1.01)		
Overweight	0.75 (0.62 -0.90)**		
Obese	1.11 (0.94 – 1.31)		
Smoking Status			
Current smoker	0.95 (0.72 – 1.24)	0.7461	0.89 (0.80 – 0.99)
Former smoker	0.94 (0.75 – 1.18)		
Never Smoked	0.85 (0.74 – 0.98)		
Diet			
Yes	1.33 (0.99 – 1.79)	0.0122	0.88 (0.79 – 0.99)
No	0.82 (0.73 – 0.93)		
Health Conditions			
Hypertension	0.87 (0.73 – 1.05)	0.8925	0.88 (0.79 – 0.98)*
CHF	0.88 (0.40 – 1.93)	0.9893	0.89 (0.79 – 0.99)*
CHD	1.48 (0.78 – 2.82)	0.1764	0.88 (0.79 – 0.98)*
Angina	1.28 (0.58 – 2.83)	0.4366	0.89 (0.79 – 0.99)*
Myocardial Infarction	1.48 (0.81 – 2.70)	0.1558	0.89 (0.80 – 0.99)*
Stroke	1.25 (0.70 – 2.26)	0.3213	0.89 (0.79 – 0.99)*
Thyroid Issues	0.85 (0.61 – 1.17)	0.8489	0.88 (0.79 – 0.98)*
Liver Disease	0..95 (0.61 – 1.47)	0.6080	1.08 (0.98 – 1.19)
* p < 0.1 ** p < 0.05 *** p < 0.01 **** p < 0.0001			

Table 2.1 shows the stratified analysis of the association between high cholesterol and depression. While no covariates had been determined to be confounders in the relationship

between high cholesterol and depression, body mass index and diet were found to be effect modifiers in the association between these two variables.

Table 2.2. Stratified analysis of the association between low cholesterol and depression

Covariate	Stratum-Specific OR (90% CI)	Breslow Day Test of Homogeneity (p-value)	Adjusted OR (90% CI)
Crude Association	0.87 (0.77 – 0.98)*		
Sex			
Male	0.90 (0.77 – 1.06)	0.9672	0.91 (0.80 – 1.02)
Female	0.91 (0.76 – 1.08)		
Age			
Young adult	0.96 (0.78 – 1.17)	0.5786	0.86 (0.76 – 0.97)
Adult	0.80 (0.62 – 1.04)		
Older Adult	0.82 (0.68 – 0.99)*		
Race/Ethnicity			
White	1.08 (0.90 – 1.30)	0.0666	0.86 (0.76 – 0.97)*
Black	0.84 (0.66 – 1.07)		
Hispanic	1.14 (0.89 – 1.46)		
Asian	1.04 (0.74 – 1.46)		
Other	0.51 (0.29 -0.88)*		
Household Income			
Less than $25,000	0.78 (0.61 – 0.99)*	0.6611	0.84 (0.74 -0.95)*
$25,000 - $55,000	0.96 (0.77 – 1.19)		
$55,000 - $99,999	0.79 (0.61 – 1.03)		
$100,000 or more	0.79 (0.59 – 1.07)		
Education			
Less than 9th grade	1.54 (0.99 – 2.41)	0.1638	0.87 (0.77 – 0.98)*
Did not finish high school	0.87 (0.61 – 1.23)		
High school grad or GED	0.71 (0.55 – 0.90)*		
Some college	0.90 (0.72 – 1.11)		
College grad or higher	0.85 (0.66 – 1.10)		
BMI			
Underweight	0.89 (0.39 – 2.02)	0.3994	0.88 (0.78 – 0.99)*
Normal	0.87 (0.69 – 1.09)		
Overweight	0.74 (0.60 – 0.92)**		
Obese	1.00 (0.83 – 1.21)		
Smoking Status			
Current smoker	0.87 (0.64 – 1.17)	0.6577	0.88 (0.78 – 0.99)*

Former smoker	0.78 (0.61 -1.01)		
Never Smoked	0.92 (0.79 – 1.07)		
Diet			
Yes	1.09 (0.81 – 1.47)	0.0795	0.82 (0.72 – 0.93)*
No	0.77 (0.67 – 0.88)***		
Health Conditions			
Hypertension	0.70 (0.57 – 0.85)***	0.0218	0.87 (0.77 – 0.97)*
CHF	0.49 (0.26 – 0.91)*	0.1185	0.86 (0.76 – 0.98)*
CHD	0.92 (0.55 – 1.54)	0.8191	0.86 (0.76 – 0.97)*
Angina	0.71 (0.36 – 1.39)	0.6267	0.86 (0.76 – 0.98)*
Myocardial Infarction	0.82 (0.50 – 1.35)	0.8275	0.87 (0.77 – 0.99)*
Stroke	0.56 (0.33 – 0.97)*	0.1750	0.87 (0.77 – 0.99)*
Thyroid Issues	0.76 (0.53 – 1.09)	0.5184	0.87 (0.76 – 0.98)*
Liver Disease	0.47 (0.26 – 0.85)	0.0801	0.86 (0.76 – 0.98)*

* p < 0.1
** p < 0.05
*** p < 0.01
**** p < 0.0001

Table 2.2 shows the stratified analysis of the association between low cholesterol and depression. Again, no covariates had been determined to be confounders in the relationship between high cholesterol and depression; however, race/ethnicity and diet were found to be effect modifiers in the association between these two variables.

Table 3.1: Multivariate Logistic Regression on the Association between High Cholesterol and Depression

	Stratum Specific Odds Ratios					
	Full Model			**Reduced Model**		
Variable	**OR**	**90% CI**	**p-value**	**OR**	**90% CI**	**p-value**
Cholesterol						
High Cholesterol	0.49	0.29 – 0.81	0.021	0.52	0.35 – 0.77	0.0068
High Cholesterol x BMI	1.19	1.02 – 1.39	0.0645	1.16	1.03 – 1.31	0.0305
High cholesterol x Diet	1.56	1.09 -2.22	0.0401	1.50	1.15 – 1.96	0.0102
Sex						
Male	0.58	0.52 – 0.68	<0.0001	0.59	0.51 – 0.67	<0.0001
Female	1.68	1.47 – 1.92	<0.0001	1.69	1.48 – 1.93	<0.0001
Age						
Young Adult	1.45	1.29 – 1.75	0.0009	1.45	1.21 – 1.74	0.0007
Adult	1.41	1.21 – 1.65	0.0003	1.39	1.19 – 1.62	0.0003
Older Adult	ref			ref		
Race/Ethnicity						
White			ref			ref

Black	0.64	0.54 – 0.76	<0.0001	0.64	0.54 – 0.76	<0.0001
Hispanic	0.74	0.61 – 0.89	0.0077	0.71	0.60 – 0.84	0.0011
Asian	0.66	0.53 – 0.81	0.0014	0.66	0.54 – 0.81	0.0010
Other	1.14	0.85 – 1.55	0.4350	1.16	0.86 – 1.57	0.3917
Household Income						
Less than $25,000	1.91	1.55 – 2.37	<0.0001	1.88	1.54 – 2.29	<0.0001
$25,000 - $55,000	1.39	1.15 – 1.68	0.0034	1.35	1.13 – 1.62	0.0048
$55,000 - $99,999	1.18	0.97 – 1.44	0.1501	1.17	0.96 – 1.42	0.1720
$100,000 or more	ref			ref		
Education						
Less than 9th grade	0.86	0.64 – 1.17	0.4364			
Did not finish high school	0.93	0.72 – 1.20	0.6781			
High school grad or GED	0.90	0.74 – 1.10	0.4141			
Some college	0.93	0.78 – 1.11	0.5145			
College grad or higher	ref					
BMI						
Underweight	0.77	0.41 – 1.44	0.4933			
Normal	ref					
Overweight	0.84	0.69 – 1.01	0.1287			
Obese	0.92	0.73 – 1.15	0.5530			
Smoking						
Current smoker	1.81	1.50 – 2.19	<0.0001	1.82	1.54 – 2.29	<0.0001
Former smoker	1.33	1.14 – 1.56	0.0024	1.33	1.14 – 1.55	0.0023
Never Smoked	ref			ref		
Diet						
Yes	0.95	0.75 – 1.22	0.7725			
No	ref					
Health Conditions						
Hypertension	1.37	1.16 – 1.61	0.0012	1.37	1.18 – 1.58	0.0003
CHF	1.43	0.87 – 2.34	0.2312	1.60	1.02 – 2.53	0.0854
CHD	0.92	0.59 – 1.45	0.7839			
Angina	1.23	0.73 – 2.064	0.5114			
Myocardial Infarction	1.24	0.81 – 1.92	0.4000			
Stroke	1.34	0.92 – 1.96	0.1946			
Thyroid Issues	1.27	1.01 – 1.60	0.0766	1.26	1.03 – 1.55	0.0535
Liver Disease	2.39	1.70 – 3.36	<0.0001	2.38	1.73 – 3.28	<0.0001
Comorbidities						
Yes	0.97	0.75 – 1.26	0.8632			

No	ref	

Table 3.1 shows the multivariate logistic regression analysis on the association between high cholesterol and depression. In the more parsimonious model, both effect modifiers were shown to increase the odds of having depression among those with high cholesterol. Other covariates that remained significant in predicting depression were: sex, age, race/ethnicity, household income, smoking, hypertension, CHF, thyroid issues, and liver disease.

Table 3.2: Multivariate Logistic Regression on the Association between High Cholesterol and Depression

Stratum Specific Odds Ratios						
	Full Model			**Reduced Model**		
Variable	**OR**	**90% CI**	**p-value**	**OR**	**90% CI**	**p-value**
Cholesterol						
Low Cholesterol	0.63	0.46 – 0.86	0.0152	0.75	0.65 – 0.88	0.0030
Low Cholesterol x Race/Ethnicity	1.08	0.96 – 1.22	0.2554			
Low cholesterol x Diet	1.42	0.98 – 2.05	0.1104	1.44	1.01 – 2.07	0.0261
Sex						
Male	0.58	0.50 – 0.67	<0.0001	0.58	0.50 – 0.67	<0.0001
Female	1.70	1.47 – 1.97	<0.0001	1.71	1.48 – 1.92	<0.0001
Age						
Young Adult	1.67	1.37 – 2.04	<0.0001	1.65	1.36 – 2.01	<0.0001
Adult	1.29	1.07 – 1.55	0.0202	1.27	1.06 – 1.53	0.0239
Older Adult	ref			ref		
Race/Ethnicity						
White	ref					
Black	0.76	0.63 – 0.92	0.0185			
Hispanic	0.82	0.74 – 1.15	0.5743			
Asian	0.74	0.57 – 0.97	0.0711			
Other	0.98	0.67 – 1.41	0.9304			
Household Income						
Less than $25,000	1.68	1.34 – 2.12	0.0002	1.68	1.36 – 2.08	<0.0001
$25,000 - $55,000	1.33	1.08 – 1.64	0.0240	1.34	1.10 – 1.64	0.0125
$55,000 - $99,999	1.21	0.98 – 1.50	0.1361	1.22	0.99 – 1.51	0.1131
$100,000 or more	ref			ref		
Education						
Less than 9th grade	1.04	0.74 – 1.45	0.8389			
Did not finish high school	0.94	0.72 – 1.24	0.7330			

High school grad or GED	0.91	0.73 – 1.13	0.5090			
Some college	0.99	0.81 -	0.9624			
College grad or higher	ref					
BMI						
Underweight	0.76	0.44 – 1.31	0.4212			
Normal	ref					
Overweight	0.88	0.72 – 1.06	0.2650			
Obese	0.94	0.79 – 1.13	0.6373			
Smoking						
Current smoker	1.96	1.60 – 2.40	<0.0001			<0.0001
Former smoker	1.23	1.03 – 1.46	0.0501			0.0231
Never Smoked	ref			ref		
Diet						
Yes	0.99	0.78 – 1.26	0.9882	1.01	0.79 – 1.28	0.9286
No	ref			ref		
Health Conditions						
Hypertension	1.29	1.08 – 1.55	0.0168	1.31	1.12 – 1.54	0.0048
CHF	1.16	0.78 – 1.73	0.5180			
CHD	1.23	0.85 – 1.76	0.3477	1.37	1.01 – 1.85	0.0809
Angina	1.16	0.73 – 1.83	0.5917			
Myocardial Infarction	0.89	0.62 – 1.29	0.6286			
Stroke	1.19	0.83 – 1.69	0.4128			
Thyroid Issues	1.24	0.98 – 1.60	0.1304	1.33	1.07 – 1.66	0.0320
Liver Disease	1.80	1.26 – 2.57	0.0068	1.92	1.37 – 2.70	0.0014
Comorbidities						
Yes	1.07	0.81 – 1.41	0.6626			
No			ref			

Table 3.2 shows the multivariate logistic regression analysis on the association between low cholesterol and depression. In the more parsimonious model, only diet was shown to increase the odds of having depression among those with low cholesterol. Other covariates that remained significant in predicting depression were: sex, age, household income, smoking, diet, hypertension, CHD, thyroid issues, and liver disease.

Discussion:

In the association between high cholesterol and depression, two effect modifiers were identified: body mass index and diet. Body mass index was shown to increase the odd of having depression among those with high cholesterol. This finding within the boundaries of this study is consistent with previous literature that revealed the role of body mass index on high cholesterol and depression. Increased body mass index has been associated with higher levels of cholesterol in conjunction with depressive symptoms, as well as an increased risk for major

depressive disorder (Parekh, et. al, 2017). On the other hand, the role of diet on high cholesterol and depression appears to contradict previous literature. In a recent RCT that assessed the effects of diet modification on depression, any dietary intervention showed beneficial outcomes on depression and mood (Firth, et. al, 2019).

In the association between low cholesterol and depression, two effect modifiers were identified: race/ethnicity and diet. However, in the reduced model, race/ethnicity was not found to be a significant in predicting depression and was therefore removed from the model. On the other hand, diet appears to increase the odds of depression among those with low cholesterol. While there are no clear answers for this association in the previous literature, some studies hypothesize that low cholesterol have an indirect role in brain serotonin levels. Serotonin receptors in the brain require a necessary supply of cholesterol to function properly, and low levels of cholesterol may indirectly affect the levels of serotonin in the brain (Steegmans, et. al, 1996). Other studies have found some consistency with this hypothesis, where a genetic syndrome resulting in low cholesterol has shown higher rates of depress (Lalovic, et. al, 2004). As a result, without adequate nutrients such a cholesterols and other lipids to optimize brain function, the findings of this study prove to be consistent with previous hypotheses and literature.

Unfortunately, the results of this study continue to add to the inconsistency of previous literature cited in the introduction. Nakao & Yano (2004) suggested that a higher prevalence of depression was displayed amongst Japanese men with cholesterol. However, the results of this study show a reduction in the odds of depression amongst men with high cholesterol (OR: 0.93, 90% CI: 0.80, 0.99). On the other hand, these results are consistent with the findings of Vilibić (2014), who revealed this protective nature in the relationship between high cholesterol and depression. Previous literature has suggested that low cholesterol yields increased odds of depression, especially among older men. Yet, this study again shows a protective effect in the association between low cholesterol and depression, especially among older men (Table 2.2).

Regardless of the results, this study displays crucial strengths that allow it to be a strong cross-sectional study. Because of the nature of the NHANES, this study was provided with a large sample size, allowing for a more accurate application to the United States population. This analysis assess numerous covariates, revealing various associations in the stratified and multivariate analysis. The health conditions analyzed in the study with respect to the association between cholesterol and depression allow for a comprehensive approach in assessing the role of morbidity and comorbidities on the effects of mental health overall.

However, there are limitations to this study. Because it is cross-sectional in nature, prevalence of depression could only be assessed. Since incidence cannot be measured due to how the NHANES survey is conducted, it is difficult to conclude if the prevalence of depression affects cholesterol levels in any ways. Furthermore, temporal ambiguity must be considered, as there is no way of telling if depression occurred before the onset of high or low cholesterol, or visa versa. The NHANES survey also introduces various levels of recall and reporting bias. Survey participants may have difficulty recalling information during the time of the interview, or may not have chosen to reveal the entire truth. Participants also have the option to refuse to answer questions, which may have affected any variables assessed in this study, thus misconstruing the true relationship between the exposure and outcome variables. Additionally, we must consider

the role of genetics in this study. NHANES does not conduct genetic testing, so it is difficult to assess the powerful role of genetics against modifiable human behavior from NHANES.

Conclusion

The results of this study show an increase in the odds of depression amongst those with high cholesterol when considering the interactions between BMI and high cholesterol, as well as diet and high cholesterol. Additionally, this study reveals increased odds of depression amongst those with low cholesterol who are dieting. This finding is crucial to understanding the inner mechanisms of brain chemistry, and point healthcare professionals in the right direction to suggest the appropriate diet for those on either end of the cholesterol spectrum. This study also highlights the importance of considering health conditions, comorbidities, and the role of genetics that may influence what interventions are given to mediate harmful cholesterol levels and depressive symptoms. Future studies should consider replicating aspects of this study in those under 18 years of age, and how the process of aging would be impacted overall. Additionally, future studies should focus on conducting more prospective studies on the relationship between high/low cholesterol and depression, with special consideration to cultural influences. Public health policy should push towards increasing physician awareness to seek out those with multiple health conditions or higher body mass index and refer them to an appropriate nutritionist, mental health, or functional medicine provider. Nutritionists and functional medicine providers should partake in continuing education courses and seminars on the association between cholesterol and depression. With this in mind, policy should also be created to enact a more streamlined network to refer patients easily between dietary, physical, and mental health professionals.

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