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Exploration of high-density lipoprotein cholesterol level and serum testosterone concentrations in adult males from NHANES, 2011——2016

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Abstract. Past explores have shown the expected linkage between high-thickness lipoprotein cholesterol (HDL-C) and testosterone fixations, yet the relationship is as yet hazy and questionable among the more extensive male populace in the U.S. The target of this review is to survey the relationship between HDL-C focuses and serum testosterone in U.S. grown-up guys. Information for this populace based study were from the Public Wellbeing and Sustenance Assessment Overview (NHANES) traversing 2011-2016. In the wake of barring grown-up guys matured under 18 years of age and without serum testosterone or HDL-C information, the example enveloped 7,804 male subjects. Contrasted and grown-ups introducing standard HDL-C levels, people with lessened HDL-C fixations displayed diminished testosterone levels ($P<0.01$). In the fundamental univariable direct relapse examination, factors including age, BMI, HDL, hemoglobin, creatinine and uric corrosive were seen to have an opposite relationship with serum testosterone levels. In the multivariate straight relapse examination, lessening serum testosterone related with decreased HDL-C focuses (assessed testosterone rate difference: 0.36% per mg/dL, $P<0.01$). In responsiveness examinations that prohibited anomaly or outrageous worth, HDL-C level was emphatically related with testosterone focuses. All in all, this cross-sectional review demonstrated a positive linkage between HDL-C levels and serum testosterone focuses in grown-up guys, and further largescale planned examinations are fundamental for approval of the causality between HDL-C and testosterone.

Keywords: Serum Testosterone, High-Density Lipoprotein Cholesterol (HDL-C), The National Health And Nutrition Examination Survey (NHANES), Linear Regression.

1. Introduction

Testosterone, a hormone predominantly synthesized by the Leydig cells in the testicle, orchestrates the development of male sexual characteristics. It plays a vital role in sperm production, bone density, muscle mass and strength. Testosterone levels naturally decrease as men age, but low levels can also be caused by certain medical conditions such as hypogonadism or diabetes. Testosterone deficiency, which affects about 7% of men in their 50s, has become a topic of growing concern and controversy around the world [1]. Testosterone additionally plays a pivotal role in the pathophysiology of metabolic disorders, and its relationship with obesity, metabolic syndrome, and type 2 diabetes

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mellitus (T2DM) have been shown in previous studies. Also, there is a bidirectional relationship between obesity and cardiovascular events [2]. Epidemiology studies indicate that diminished testosterone levels correlate with increased prevalence of atherosclerosis and coronary artery disease. In addition, androgen deficient men also show increased fat accumulation, reduced muscle and mineral bone mass, which illustrate a parallel between male reproductive function and obesity. Testosterone replacement therapy serves as a therapeutic intervention for males exhibiting reduced testosterone concentrations, and it can produce significant attenuation in the weight loss–induced reduction in muscle mass, improvement in insulin resistance and hyperlipidemia [3, 4].

High-density lipoprotein (HDL), a set of biological molecules, plays a multiple role in metabolism, regulation and homeostasis in the human body [5]. HDL is composed of proteins and lipids, with the characteristics of diminutive molecular size and elevated density. Its primary function is to facilitate the transfer of cholesterol from peripheral blood to the liver for metabolism and assimilation, called the reverse transport of cholesterol which mitigates cholesterol accrual within the body (Figure 1) [6]. Furthermore, HDL has antioxidant properties, with paraoxonase 1 (PON1) and apolipoprotein AI (APOAI) potentially serving as the principal antioxidant constituents. HDL encompasses a diverse array of lipid/protein complexes of varying sizes and hundreds of different lipid particles [7]. One of these components is cholesterol, and the part of cholesterol carried in HDL particles is called high-density lipoprotein cholesterol (HDL-C). In actual clinical practice HDL-C is measured to reflect the level of cholesterol in the body. In some relevant researches its reverse transport of cholesterol, antioxidant, anti-inflammation, and antithrombotic actions contribute to the reduction of cardiovascular disease (CVD) risk, while a contemporary investigation noted a U-shaped correlation between HDL-C concentrations and CVD mortality [8, 9].

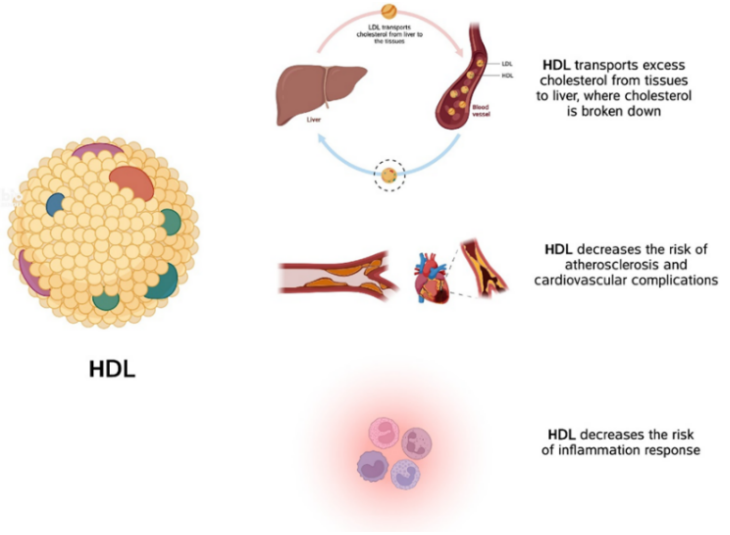

Figure 1. Summary of the normal function of high-density lipoprotein (HDL) [6].

Among previous studies, the association between HDL-C and serum testosterone levels remain contentious and the results lack of high-level research evidence. Low testosterone concentrations are proved to improve the risk of metabolic syndrome and dyslipidemia, both of which are linked with low HDL-C level, so testosterone level might positively relate to HDL-C. Also, some studies suggest that elevated testosterone serves as a risk determinant for vascular diseases, underscoring a positive association between HDL-C and testosterone levels [10, 11]. However, there are also some opposite conclusion [12, 13]. Therefore, in this cross-sectional analysis, data sourced from the National Health and Nutrition Examination Survey (NHANES) were used to investigate the association between the HDL-C and testosterone.

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2. Methods

2.1. Data source and object of the study

The NHANES, led biennially by the Public Place for Wellbeing Insights (NCHS), is a broadly cross-sectional intended to assess the wellbeing or dietary profiles of U.S. populace [14]. The review involved a family interview followed by a normalized wellbeing evaluation at a reason constructed versatile assessment office. Additionally, the evaluation included specific laboratory diagnostics and a skilled medically conducted physical examination [15]. The NCHS research ethics board approved the NHANES operational protocols in accordance with the 2013 amendments to the Declaration of Helsinki [16]. All members gave composed informed assent. Hence, the Public Place for Wellbeing Insights anonymized all information before open delivery.

2.2. Study Design and Population

The analyses were based on data accrued from three biennial NHANES cycles spanning 2013 – 2014, 2015 – 2016, and 2017 – 2018. From an initial participant pool (n=29,902), exclusions were made based on the subsequent criteria: individuals below 18 years of age (n=11,933); absent data on serum testosterone (n=1,891) and HDL-C (n=3); and female participants' data (n=8,271). The flowchart for participant enrollment is presented in Figure 2

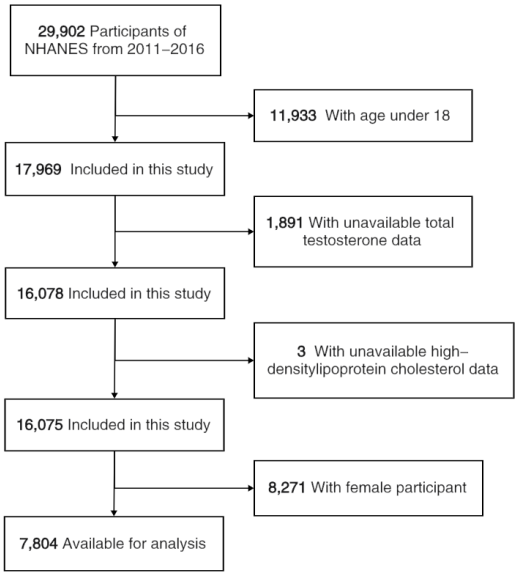

Figure 2. Flow diagram of the screening and enrollment of eligible participants.

2.3. Study variables

On the Roche/Hitachi Modular P Chemistry Analyzer, an endpoint method was used to measure HDL-C [17]. Serum testosterone levels were measured by utilizing isotope weakening fluid chromatography pair mass spectrometry (ID-LC-MS/MS), as indicated by the reference technique for the Public Establishment of Norms and Innovation (NIST) [18]. Because clinically low testosterone is diagnosed in individuals with total testosterone levels below 300 ng/dl [19], eligible participants were divided into two cohorts. Adults with testosterone levels below 300 ng/dL were included in the group with low testosterone levels, while the rest of the group had testosterone levels that were considered normal.

In view of the writing [21-23], the accompanying covariates were incorporated: age, race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Dark, and Other Race), BMI (underweight: less than 18.5 kg/m2; normal: ranging from 18.5 to 25 kg/m2; overweight: somewhere in the range of 25 and 30 kg/m2; obesity: over 30 kg/m2) [20], low-thickness lipoprotein cholesterol

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(LDL-C), serum creatinine, serum uric corrosive (SUA) and fatty oils. A questionnaire that asked participants to self-report having been diagnosed with hypertension or diabetes by a doctor was used to collect the history of hypertension or diabetes.

2.4. Statistical analysis

All analyses were conducted in accordance with the NHANES analytic guidelines [24] and included weighting variables to ensure that estimates were nationally representative. The survey design's adjusted sample weight was calculated by dividing the original 2-year sample weight by 3. Distributed (continuous) variables were described using the median (interquartile range). The t tests worked with examinations of persistent information, and the chi-square test evaluated absolute information. Means for categorical variables and quartiles for continuous variables were used to describe the study cohort's demographic characteristics.

The relationship between each independent variable and testosterone was evaluated using multivariate linear regression models. Given the right-slanted appropriation, testosterone focuses were log-changed for the relapse examination, and relapse coefficients, standard blunders and P values were determined for subordinate variable. Participants with extreme values (serum testosterone concentrations below 50 ng/dL or above 1000 ng/dL) and outliers (values exceeding 3 standard deviations from the mean) were excluded from the analysis to ensure the robustness of the findings.

R 4.3.0 and R Studio were used for the statistical analyses. In all assessments, a two-sided P-esteem under 0.05 was considered characteristic of factual importance.

3. Results

3.1. Characteristics of the Participants

Table 1 shows the demographics of participants among different HDL-C levels. The study encompassed 7,804 participants, who were segmented into four groups based on HDL-C quartiles: Q1 (6< HDL-C ≤339 mg/dL), Q2 (40< HDL-C ≤46 mg/dL), Q3 (447< HDL-C ≤55 mg/dL) and Q4 (56< HDL-C ≤173 mg/dL), and the average HDL-C concentration was 48.23±14.27 mg/dL. When adjusted for weighting, the average age of 7,804 participants stood at 47.63±18.51 years, with an average serum testosterone level of 417.12±189.54 ng/dL. Noteworthy statistical disparities were evident across the quartile groups in terms of variables such as age, race, BMI, total cholesterol, triglyceride, LDL-C, hemoglobin, serum uric acid, testosterone, prevalence of hypertension and diabetes.

Table 1. Characteristics of participants in different HDL-C levels from NHANES 2011–2016 cycle.

Characteristics	High-density lipoprotein cholesterol quartiles				
	Q1	Q2	Q3	Q4	P value
Number of subjects (%)	2176	1879	1854	1895	
Age (year)‡	47.00 [33.00, 61.00]	47.00 [31.00, 62.00]	46.00 [30.00, 62.00]	51.00 [32.00, 65.00]	<0.001
Race (%)†					<0.001
Mexican American	359 (16.5)	306 (16.3)	245 (13.2)	203 (10.7)	
Other Hispanic	260 (11.9)	188 (10.0)	180 (9.7)	133 (7.0)	
Non-Hispanic White	896 (41.2)	709 (37.7)	707 (38.1)	690 (36.4)	
Non-Hispanic Black	331 (15.2)	362 (19.3)	399 (21.5)	584 (30.8)	
Other Race	330 (15.2)	314 (16.7)	323 (17.4)	285 (15.0)	

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Table 1. (continued).

Body mass index (%)†					<0.001
Underweight: BMI <18.5 (kg/m2)	8 (0.4)	17 (0.9)	31 (1.7)	51 (2.7)	
Normal: BMI ≥18.5 and <25 (kg/m2)	307 (14.3)	423 (22.8)	599 (32.6)	873 (46.5)	
Overweight: BMI ≥25 and <30 (kg/m2)	1042 (48.7)	701 (37.7)	519 (28.2)	304 (16.2)	
Obesity: BMI ≥30 (kg/m2)	783 (36.6)	716 (38.6)	689 (37.5)	651 (34.6)	
Total Cholesterol (mg/dL)‡	179.00 [150.00, 210.00]	182.00 [155.00, 211.00]	183.00 [157.00, 210.75]	188.00 [163.00, 213.50]	<0.001
Triglyceride (mg/dL)‡	155.00 [105.00, 240.00]	115.00 [84.75, 166.00]	90.00 [67.00, 125.25]	72.00 [53.00, 96.00]	<0.001
Low-density lipoprotein cholesterol (mg/dL)‡	105.00 [80.00, 130.50]	112.00 [88.00, 137.00]	109.00 [88.00, 134.00]	105.00 [83.00, 130.00]	<0.001
Hemoglobin (g/dL) ‡	15.00 [14.10, 15.80]	15.00 [14.20, 15.60]	14.90 [14.10, 15.60]	14.70 [13.90, 15.50]	<0.001
Serum creatinine (mg/dL)‡	0.96 [0.85, 1.11]	0.96 [0.84, 1.09]	0.96 [0.86, 1.09]	0.96 [0.85, 1.10]	0.679
Serum uric acid (mg/dL)‡	6.20 [5.40, 7.10]	6.00 [5.20, 6.90]	5.80 [5.10, 6.70]	5.70 [4.90, 6.50]	<0.001
High-density lipoprotein cholesterol (mg/dL)‡	35.00 [31.00, 37.00]	43.00 [41.00, 45.00]	50.00 [48.00, 53.00]	64.00 [59.00, 72.00]	<0.001
High-density lipoprotein cholesterol (mmol/L)‡	0.91 [0.80, 0.96]	1.11 [1.06, 1.16]	1.29 [1.24, 1.37]	1.66 [1.53, 1.86]	<0.001
Testosterone (ng/dL)‡	330.00 [248.46, 434.23]	369.00 [284.00, 491.00]	411.08 [312.00, 530.80]	462.89 [345.76, 599.00]	<0.001
Hypertension (%)†					<0.001
Yes	842 (38.7)	630 (33.5)	617 (33.3)	601 (31.7)	
No	1329 (61.1)	1248 (66.4)	1235 (66.6)	1292 (68.2)	
Don’t know	5 (0.2)	1 (0.1)	2 (0.1)	2 (0.1)	
Diabetes (%)†					<0.001
Yes	409 (18.8)	266 (14.2)	201 (10.8)	182 (9.6)	
No	1701 (78.2)	1570 (83.6)	1612 (86.9)	1673 (88.3)	
Borderline	66 (3.0)	42 (2.2)	39 (2.1)	39 (2.1)	
Don’t know	0 (0.0)	1 (0.1)	2 (0.1)	1 (0.1)	

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Data are represented as either the count of subjects (percentage) or medians (interquartile ranges). †, Chi-square test was utilized for comparing proportions of categorical data; ‡, t test was utilized to contrast the median values of continuous data. Q1 (6< HDL-C ≤339 mg/dL), Q2 (40< HDL-C ≤46 mg/dL), Q3 (447< HDL-C ≤55 mg/dL) and Q4 (56< HDL-C ≤173 mg/dL).

Table 2 displays the characteristics of participants stratified by varying testosterone levels. The prevalence of low testosterone concentrations was higher among people with low HDL-C level (mean concentrations, 1.09 mmol/L; IQR, 0.91-1.29) than people with normal HDL-C level (mean concentrations, 1.24 mmol/L; IQR, 1.03-1.47) and among participants who were older (52.00 [37.00, 66.00] vs 45.00 [30.00, 61.00]). In addition, participants exhibiting lower testosterone levels tended to have lower hemoglobin (g/dL) (14.60 [13.70, 15.40] vs 15.00 [14.20, 15.80]), higher triglyceride (mg/dL) (131.50 [87.00, 196.00] vs 95.00 [67.00, 144.00]) and SUA (mg/dL) (6.30 [5.40, 7.20] vs 5.80 [5.10, 6.70]), also a lower prevalence of obesity, hypertension and diabetes.

Table 2. Participant characteristics stratified by serum testosterone levels from NHANES 2011–2016 cycle.

Characteristics	Low testosterone level	Normal testosterone level	P value
Number of subjects (%)	2145	5659	
Age (year)‡	52.00 [37.00, 66.00]	45.00 [30.00, 61.00]	<0.001
Race (%)†			0.058
Mexican American	306 (14.3)	807 (14.3)	
Other Hispanic	215 (10.0)	546 (9.6)	
Non-Hispanic White	873 (40.7)	2129 (37.6)	
Non-Hispanic Black	426 (19.9)	1250 (22.1)	
Other Race	325 (15.2)	927 (16.4)	
Body mass index (%)†			<0.001
Underweight: BMI <18.5 (kg/m2)	10 (0.5)	97 (1.7)	
Normal: BMI ≥18.5 and <25 (kg/m2)	277 (13.1)	1925 (34.3)	
Overweight: BMI ≥25 and <30 (kg/m2)	1102 (52.3)	1464 (26.1)	
Obesity: BMI ≥30 (kg/m2)	719 (34.1)	2120 (37.8)	
Total Cholesterol (mg/dL)‡	183.00 [156.00, 213.00]	183.00 [157.00, 211.00]	0.504
Triglyceride (mg/dL)‡	131.50 [87.00, 196.00]	95.00 [67.00, 144.00]	<0.001
Low-density lipoprotein cholesterol (mg/dL)‡	105.00 [78.75, 131.00]	109.00 [86.00, 134.00]	0.016
Hemoglobin (g/dL) ‡	14.60[13.70, 15.40]	15.00 [14.20, 15.80]	<0.001
Serum creatinine (mg/dL)‡	0.97 [0.85, 1.13]	0.96 [0.85, 1.08]	<0.001
Serum uric acid (mg/dL)‡	6.30 [5.40, 7.20]	5.80 [5.10, 6.70]	<0.001
High-density lipoprotein cholesterol (mg/dL)	42.00 [35.00, 50.00]	48.00 [40.00, 57.00]	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.09 [0.91, 1.29]	1.24 [1.03, 1.47]	<0.001

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Table 2. (continued).

Testosterone (ng/dL)‡	235.00 [189.75, 269.00]	452.00 [369.03, 564.21]	<0.001
Hypertension (%)†			<0.001
Yes	962 (44.8)	1728 (30.5)	
No	1181 (55.1)	3923 (69.3)	
Don't know	2 (0.1)	8 (0.1)	
Diabetes (%)†			<0.001
Yes	470 (21.9)	588 (10.4)	
No	1598 (74.5)	4958 (87.6)	
Borderline	76 (3.5)	110 (1.9)	
Don't know	1 (0.0)	3 (0.1)	

Data are represented as either the count of subjects (percentage) or medians (interquartile ranges). †, Chi-square test was utilized for comparing proportions of categorical data; ‡, t test was utilized to contrast the median values of continuous data. Q1 (6< HDL-C ≤339 mg/dL), Q2 (40< HDL-C ≤46 mg/dL), Q3 (447< HDL-C ≤55 mg/dL) and Q4 (56< HDL-C ≤173 mg/dL).

3.2. Univariable Regression Analyses

Table 3 blueprints the connections between every free factor and log-changed testosterone in light of univariable direct relapse examination. In model 1, a positive relationship arose between HDL-C, hemoglobin and serum testosterone separately. Conversely, testosterone had a significant negative correlation with age, BMI, creatinine, and uric acid. Responsiveness examinations, which precluded members with exception or outrageous qualities, were led, and the positive relationship between's HDL-C and serum testosterone endured in model 2.

Table 3. The results from the univariable linear regression analysis of log-transformed serum testosterone based on NHANES 2011–2016 cycle.

Variable	Model 1				Model 2			
	R2	B	SE	P value	R2	B	SE	P value
Age (years)	0.036	-0.006	<0.001	<0.001	0.039	-0.006	<0.001	<0.001
Race	0.002				0.001			
Mexican American			0.017	<0.001			0.016	<0.001
Other Hispanic		0.017	0.026	0.511		0.017	0.026	0.754
Non-Hispanic White		-0.014	0.019	0.461		-0.017	0.019	0.371
Non-Hispanic Black		.035	0.021	0.100		0.023	0.021	0.286
Other Race		0.039	0.023	0.090		0.035	0.022	0.117
BMI (kg/m2)	0.114	-0.030	<0.001	<0.001	0.112	-0.029	<0.001	<0.001
HDL-C (mg/dL)	0.043	0.008	<0.001	<0.001	0.042	0.008	<0.001	<0.001
LDL-C (mg/dL)	0.003	<0.001	<0.001	0.002	0.003	<0.001	<0.001	0.002
Hemoglobin (g/dL)	0.026	0.094	0.005	<0.001	0.049	0.090	0.005	<0.001
Creatinine (mg/dL)	0.008	-0.105	0.013	<0.001	0.008	-0.103	0.013	<0.001
Uric acid (mg/dL)	0.022	-0.062	0.005	<0.001	0.020	-0.059	0.005	<0.001
Hypertension	0.026				0.029			

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Table 3. (continued).

Yes			0.011	<0.001			0.010	<0.001
No		0.190	0.013	<0.001		0.196	0.013	<0.001
Diabetes	0.322				0.031			
Yes			0.017	<0.001			0.017	<0.001
No		0.285	0.018	<0.001		0.280	0.018	<0.001

In Table 3, Model 1 is no adjustment for potential confounders. Model 2 is adjusted by excluding participants exhibiting outlier or extreme value. R^2 means coefficient of determination. B means unstandardized regression coefficient; SE, standard error of the coefficient.

3.3. Multivariable Regression Analyses

In multivariate linear regression, serum testosterone was inversely associated with age (estimated testosterone percentage variance: -0.31% per year, P<0.01), BMI (estimated testosterone percentage variance: -2.81% per kg/m2, P<0.01), and SUA (estimated testosterone percentage variance: -1.95% per mg/dL, P<0.01). A positive relationship of hemoglobin (estimated testosterone percentage variance: 9.12% per g/dL, P<0.01), HDL-C (estimated testosterone percentage variance: 0.36% per mg/dL, P<0.01) and serum testosterone were revealed in model 1. The positive correlation between HDL-C and serum testosterone remained statistically significant in model 2.

Table 4. The results from the multivariate linear regression analysis of log-transformed serum testosterone based on NHANES 2011–2016 cycle.

Variable	Model 1				Model 2			
	Adj. R2	B	SE	P value	Adj. R2	B	SE	P value
Age (years)	0.224	-0.003	<0.001	<0.001	0.226	-0.003	<0.001	<0.001
Race								
Mexican American								
Other Hispanic		-0.004	0.033	0.894		-0.016	0.033	0.618
Non-Hispanic White		-0.040	0.026	0.119		-0.038	0.025	0.129
Non-Hispanic Black		0.047	0.029	0.111		0.033	0.029	0.258
Other Race		-0.057	0.030	0.061		-0.058	0.030	0.051
BMI (kg/m2)		-0.028	0.002	<0.001		-0.029	0.002	<0.001
HDL (mg/dL)		0.004	<0.001	<0.001		0.004	<0.001	<0.001
LDL ()		<0.001	<0.001	0.024		<0.001	<0.001	0.016
Hemoglobin		0.087	0.007	<0.001		0.084	0.007	<0.001
Creatinine		-0.012	0.016	0.480		-0.008	0.016	0.613
Uric acid		-0.020	0.007	0.003		-0.016	0.007	0.017
Hypertension								
Yes								
No		0.016	0.020	0.424		0.023	0.019	0.232
Diabetes								
Yes								
No		0.063	0.026	0.018		0.061	0.026	0.019

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Model 1 is no adjustment for potential confounders. Model 2 is adjusted by excluding participants exhibiting outlier or extreme value. R2 means adjusted coefficient of determination; B means unstandardized regression coefficient. SEmeans standard error of the coefficient.

4. Discussion

This study identified a positive correlation between HDL-C and serum testosterone in both univariable and multivariate linear regression analyses. After omitting participants presenting outlier or extreme value, the relationship still remained.

Some previous studies illustrated the possibly biological mechanisms between serum testosterone and HDL. It has been confirmed that low baseline testosterone level is related to insulin resistance as well as obesity, which are risk factors for CVD [25, 26]. Insulin resistance have been associated with enhancive exchange of triglyceride from chylomicrons and very low-density lipoprotein for cholesterol esters from HDL particles, thus reducing HDL-C [27]. In addition, HDL is involved in the reverse transport of cholesterol from peripheral tissue to the liver, which can prevent the oxidation of LDL cholesterol and the adverse effects of oxidized LDL on endothelial cells, finally leading to the increase of testosterone concentrations [28, 29]. In conclusion, obesity, CVD and insulin resistance may mediate the correlation between serum testosterone and HDL-C.

A cross-sectional study conducted by Rovira [10] indicated that diabetic men with low testosterone levels probably have impaired metabolism and decreased HDL and LDL, which puts patients at risk for CVD. The result is consistent with this finding. However, there is also some controversial evidence. An intracranial aneurysm (IA) model conducted by Tao pointed out that testosterone aggravated cerebral vascular injury by reducing plasma HDL levels [12]. Also, over 12-months of testosterone treatment for hypogonadal men, there was a significant decrease in HDL-C level and an improvement in dihydrotestosterone [13].

Compared with previous studies investigating the relationship between serum testosterone and HDL-C using relatively small sample sizes, this investigation employed a substantial, nationally representative sample of the general U.S. population aged 18 and above. Furthermore, this analysis utilized diverse statistical methodologies and was meticulously adjusted for potential confounders, enhancing the reliability of the findings.

In any case, the ongoing review isn't without restrictions. First, the cross-sectional study made it difficult to prove a link between HDL-C and testosterone. Second, recording at least two values on distinct days is the gold standard for diagnosing low testosterone. Additionally, since testosterone and HDL levels are dynamic variables, the measurement process is subject to bias. Third, the possible impacts of free or bioactive testosterone on HDL-C were not viewed as in this examination while breaking down the relationship between HDL-C and testosterone.

5. Conclusion

This review shows a positive relationship between's HDL-C and serum testosterone levels in grown-up guys from the overall U.S. populace. It emphasizes the need for additional longitudinal research to clarify the mechanisms by which HDL-C and testosterone are linked. Also, this relationship might offer significant bits of knowledge for working on the administration of cardiovascular illnesses and testosterone lack.

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