Journal of Clinical Lipidology (2011) 5, 173–178

Journal of Clinical Lipidology

Age is positively associated with high-density lipoprotein cholesterol among African Americans in cross-sectional analysis: The Jackson Heart Study

Jane L. Harman, DVM, PhD*, Michael E. Griswold, PhD, Neal O. Jeffries, PhD, Anne E. Sumner, MD, Daniel F. Sarpong, PhD, Ermeg L. Akylbekova, MS, Evelyn R. Walker, MD, MPH, Sharon B. Wyatt, RN, PhD, Herman A. Taylor Jr., MD, MPH

Program in Prevention and Population Sciences, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, 6701 Rockledge Drive, Suite 10018, Bethesda, MD 20982–7936, USA (Dr. Harman); University of Mississippi Medical Center, Jackson, MS (Dr. Griswold); Office of Biostatistics Research, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA (Dr. Jeffries); Program in Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD, USA (Dr. Walker); National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA (Dr. Sumner); Jackson State University, Jackson, MS, USA (Drs. Sarpong and Taylor; and E. L. Akylbekova); University of Mississippi Medical Center, Jackson, MS, USA (Drs. Wyatt and Taylor); and Tougaloo College, Tougaloo, MS, USA (Dr. Taylor)

KEYWORDS:
African Americans;
Aging;
Cohort studies;
Epidemiology;
High-density lipoprotein cholesterol;
Triglycerides

BACKGROUND: African Americans have historically had high high-density lipoprotein cholesterol (HDL-C) compared with other races and ethnicities.

OBJECTIVE: We sought to characterize whether there is a cross-sectional association between age and HDL-C in a contemporary community-based study of African Americans.

METHODS: Cross-sectional data were modeled by logistic regression for predictors of HDL-C among African Americans, ages 35–74, participating in the baseline examination of a community-based study of cardiovascular disease in Jackson, Mississippi, during 2000–2004. After excluding persons taking lipid-lowering medications, hormone replacement therapy, oral contraceptives, or thyroid replacement, the analytical data set comprised 2420 persons (1370 women, 1050 men).

RESULTS: HDL-C had a significant positive association with age after controlling for serum triglycerides, sex, waist circumference, percent dietary calories from carbohydrates, alcohol use, and leisure physical activity. Sex was a significant effect modifier of this relationship, whereby the increase in HDL-C with age was steeper for women than for men.

CONCLUSIONS: Cross-sectional analysis found a positive association of HDL-C with age while controlling for triglycerides. Careful evaluation of longitudinal data will be needed to confirm whether this is a true effect of aging, or a cohort or survivor effect.

Published by Elseiver Inc on behalf of National Lipid Association.

* Corresponding author.
E-mail address: harmanj@mail.nih.gov

Submitted November 1, 2010. Accepted for publication February 2, 2011.

African Americans have greater mortality from coronary heart disease (CHD) compared with white or and Hispanic Americans.[1] However, until the mid-1980s, African

1933-2874/$ - see front matter Published by Elseiver Inc on behalf of National Lipid Association.
doi:10.1016/j.jacl.2011.02.002

Americans had a lower risk of death from CHD than white Americans of the same sex,[2,3] with a favorable risk profile typically characterized by greater levels of high-density lipoprotein-cholesterol (HDL-C) compared with white subjects.[4,5] The historically higher HDL-C among African Americans may have been related to the intensity of occupational physical activity of past occupations of African Americans, particularly among men.[6] High protective levels of HDL-C may become less prevalent among younger African Americans who are now working at predominantly sedentary occupations. We sought to determine whether age was associated with HDL-C among a contemporary sample of African Americans.

Cross-sectional and longitudinal studies of the association of HDL-C with age have generally focused on European, white American, or Asian populations.[7–15] Cross-sectional studies in these populations have generally noted that HDL-C is stable across age groups[7,8] or slightly increasing with age among women;[9] occasionally, the authors of cross-sectional studies have noted an increase with age in both sexes.[15] Several longitudinal analyses of HDL-C have shown stable or decreasing values of HDL-C with age, but these decreases were associated with weight gain or an increase in triglycerides[10–13]; fewer longitudinal studies have shown an increase with age.[14,16] Up to this time, there have been no large studies of HDL-C across age groups among African Americans. The Jackson Heart Study (JHS) provides an opportunity to investigate the association of age with HDL-C in a large community-based cohort of African Americans.

We sought to characterize the association of serum \HDL-C with age among African Americans, ages 35–74, from the JHS after controlling for important covariates, including serum triglycerides (TG). HDL-C levels are inversely related to TG levels, as cholesterol ester transferase protein (CETP) exchanges cholesterol esters attached to HDL particles for TG from TG-rich lipoproteins, especially from very low-density lipoprotein.[17] Therefore, any description of independent determinants of HDL-C must control for TG.

Methods

The JHS is a longitudinal community-based study of the determinants and trajectory of cardiovascular disease among 5301 adult African Americans in the Jackson, Mississippi, metropolitan area.[18] All participants gave their informed consent to this study, approved by the institutional review boards of Jackson State University, the University of Mississippi Medical Center, and Tougaloo College. At the first clinical examination during 2000–2004, blood pressure and anthropometric measures were obtained and blood samples were drawn after an 8-hour fast. HDL-C was measured in serum after Mg-dextran precipitation of serum (Roche Diagnostics, Indianapolis, IN); laboratory coefficient of variation for HDL-C was 2.9%.

In an accompanying interview, the participants reported their physical activity, current medications, usual dietary intake, alcohol and tobacco use, level of educational attainment, and usual occupation (if retired, their usual preretirement occupation); women reported their menstrual history. The level of physical activity required by the participant's usual occupation was categorized as either sedentary, mostly standing, or strenuous.[19]

Of the 5301 participants in the first JHS examination, 4741 were between the ages of 35–74; sequential exclusions were of participants taking thyroid medication (243), having invalid dietary data (438), missing data on lipid-lowering medications (354), taking lipid-lowering medications (521), women missing menstrual or hormone medications status (27), and women taking oral contraceptives or hormone replacement therapy (496). Additional sequential exclusions were of those participants missing data on serum HDL-C (229), serum TG (1), waist circumference (6), and those with extreme outlier lipid values: TG ≥700 (3), low-density lipoprotein ≥300 (1), HDL ≥130 (2). The resulting analysis set comprised 2420 persons: 1370 women and 1050 men (Table 1). Of the 1370 women, 875 were considered postmenopausal, ie, they reported no menstrual periods during the past 2 years.

Table 1 Description of analytical population, ages 35–74 years, Jackson Heart Study Baseline Exam, 2000–2004, n = 2420*

	Women n = 1370	Men n = 1050
Age	53.8 (10.7)	53.4 (10.2)
HDL-C, mg/dL	53.4 (13.6)	45.8 (12.2)
Triglycerides, mg/dL	95.1 (53.9)	111.2 (66.8)
BMI	33.0 (7.5)	29.8 (6.0)
Waist, cm	100.3 (17.0)	100.7 (14.2)
% dietary calories as carbohydrates	51.1 (9.4)	49.5 (9.0)
Physical activity score†	8.4 (2.5)	8.8 (2.5)
Any alcohol use during past year	38%	61%
Hypertensive	56%	56%

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.
Values are mean (SD).
*Excluded participants taking lipid-lowering or thyroid medications, hormone replacement, or oral contraceptives.
†Composite of four domains of physical activity, range 0–20.

Data evaluations were conducted for all men and women; women only; men only; and men and women ≥ age 45 years wherein women were restricted to those who were postmenopausal. Visual examinations guided decisions on data transformations and functional relationship formulations. Logarithmic (base 2) transformation was performed on TG. Waist circumference, as a measure of body adiposity, was more strongly correlated with HDL-C than body mass index and was offered to regression models. The following independent predictors were examined in each model: age, sex (and menopausal status for women-only model), log2 (TG), non-HDL cholesterol, waist circumference, total dietary calories, percent of calories from carbohydrate, and the following dichotomous variables: leisure and household physical activity score above the 90th percentile, sedentary occupation, hypertension (systolic blood pressure >140 or diastolic >90 or taking anti-hypertensive medication), any current alcohol use, any current tobacco use, and noncompletion of high school. Because low HDL-C has been associated with uricemia[20] and with insulin resistance,[21,22] these models of HDL-C were also offered terms for the values of serum uric acid and HbA1C.

For each population subgroup examined, unadjusted, fully adjusted, and parsimonious models were examined. We present results for the association of age and HDL-C from the parsimonious model that explained the greatest proportion of the population variation in HDL-C. Models were fit with the use of generalized estimating equations,[23] to account for associations arising from the existence of siblings in the study. For each selected final model, randomness of residuals was ascertained for all covariates. SAS v9.2 was used for all analyses (SAS Institute, Cary, NC).

Results

Younger persons were significantly more likely than older persons to report usual occupations classified as sedentary: 56% of ages 35–44 reported sedentary occupations, decreasing to 29% of ages 65–74 (Cochran-Armitage Trend Test, $P < .001$).

In all regression models, four covariates explained approximately 90% of the modeled variation in HDL-C: sex, TG, age, and waist circumference. As expected, male sex, TG, and waist circumference were all negatively associated with HDL-C.

Age accounted for approximately 10% of this modeled variation and was significantly and positively associated with HDL-C in the final multivariable models. Age was a significant predictor of HDL-C in the model with all persons (Table 2) as well as when the model was restricted to either sex (results not shown) or restricted to men and postmenopausal women of ages 45+ (results not shown). For the model using data from all persons, an interaction term for age-by-sex was also significant, with women showing a faster rate of increase in HDL-C with age than men (0.34 ± .05 mg/dL vs. 0.13 ± .04 mg/dL, per year of age; Table 2 and Figure 1).

Alcohol use, leisure physical activity level above sex-specific 90th percentile (both positively associated with HDL-C), and percent of dietary calories from carbohydrate (negatively associated with HDL-C) were significant predictors in the model that used data from all men and women, but these covariates explained little of the modeled variance in HDL-C; sedentary occupation was negatively associated with HDL-C, but its effect did not reach significance.

Upon controlling for the aforementioned covariates, we found that none of these remaining covariates offered to the multivariable models were retained as significantly related to HDL-C: hemoglobin A1C, uric acid, total dietary calories, tobacco use, or noncompletion of high school. In the model restricted to women, menopausal status was not a significant predictor of HDL-C, after controlling for TG, waist, and non-HDL cholesterol.

Discussion

In this cross-sectional analysis of data from African-American adults, HDL-C was significantly greater in older persons, after controlling for sex, TG, waist circumference, and several other significant but less important predictors of HDL-C. Age was significantly predictive of greater HDL-C, whether using the entire analytical data set of ages 35–74, or restricting the data either to persons age 45+ or to a single sex. We also determined that there was a significant interaction by sex, such that for women there was a greater increase in HDL-C per year of age difference than among men.

In cross-sectional studies of HDL-C in other populations, most have described stable HDL-C levels with age, but TG was not controlled in these analyses.[7,8] Heitman, [9] using cross-sectional data from Danish adults, found that HDL-C increased with age in women but not men. The authors[15] of a recent cross-sectional study in China of 3914 adults found a positive association between age and HDL-C for both sexes: the prevalence of low HDL-C steadily was higher in young adults than in older adults.

Longitudinal studies evaluating the association of HDL-C with aging have usually found that HDL-C decreased or was stable with aging. In these populations, TG also increased with aging, or the changes in TG were not reported.[10–13,24,25] In contrast to these findings, the present cross-sectional analysis may reflect an increase with HDL-C that occurs with aging after controlling for TG; because these aforementioned longitudinal analyses of HDL-C did not control for longitudinal changes in TG, it is not surprising that these earlier reports do not comport with our findings.

There have been two notable exceptions whereby longitudinal studies have reported that HDL-C increases with aging. Among Japanese-American men from the Honolulu Heart Study, the HDL-C increased significantly during a 20-year period, wherein increasing HDL-C was associated

Table 2 The association of HDL-C, mg/dL, with age and sex, men and women, ages 35–74, Jackson Heart Study Baseline Exam, 2000-2004, n = 2420*

Parameter†	Estimate	95% Confidence Limits	Pr >|Z|
Intercept	44.2	43.3, 45.1	<.0001
Female	7.1	6.2, 8.1	<.0001
Age, per year	0.13	.06, .20	.0003
Female*Age†	0.21	0.12, 0.30	<.0001
Triglyceride, per doubling, mg/dL	−7.1	−7.8, −6.4	<.0001
Waist, per cm	−0.15	−0.18, −0.12	<.0001
Dietary carbohydrate, per % dietary calories	−0.10	−0.15, −0.05	.0001
Alcohol use, any vs. none	2.0	1.0–3.0	<.0001
Leisure physical activity, above 90th pctle vs. below	1.8	0.41–3.2	.0109

*Excluded participants taking lipid-lowering or thyroid medications, female hormone replacement or oral contraceptives. 2283 obs used in regression; 135 obs missing data on physical activity, 2 obs missing data on alcohol use. SAS Proc GenMod, GEE analysis accounted for 2120 sibling clusters.

†Continuous covariates were centered at the following values: age = 55 years, triglycerides = 100 mg/dl, waist = 100 cm, dietary carbohydrates = 50% of dietary calories. Thus, the intercept value (44.2 mg/dL) represents the mean estimate of HDL-C for a 55-year-old man who does not drink alcohol, is not in the upper decile of physical activity, and for whom all other covariates equal the centered values.

with decreasing body weight; the longitudinal change in TG was not reported.[16] Early longitudinal analysis from mid-1970s to early 1980s of young, white adults in the Framingham Offspring cohort had reported HDL-C decreasing with aging but with no mention of TG changes[13]; however, later longitudinal analysis of serial examinations conducted between 1991–2001of this same cohort, now older, reported a longitudinal rise in mean HDL-C coupled with a decline in TG; the relationship between HDL-C and TG by age was not explicitly assessed.[14] The Framingham authors reasoned that these later changes in HDL-C and TG could be attributed to change in the U.S. diet from saturated to nonsaturated dietary lipids during the 1990s.[14]

Similar to our own analysis, one other report explicitly controlled for TG in an analysis of the effect of age on HDL-C, using data from two cross-sectional studies, one each from the United States and Hong Kong. In univariate analysis of these data, HDL-C appeared to be decreasing with age among Hong Kong women. However, similar to our own results, multivariable analysis that controlled for TG and other covariates found that the odds of low HDL decreased with higher age, ie, that HDL increased with age, in both U.S. and Hong Kong women and in U.S. men; only among Hong Kong men was there was no significant effect of age on HDL-C.[26]

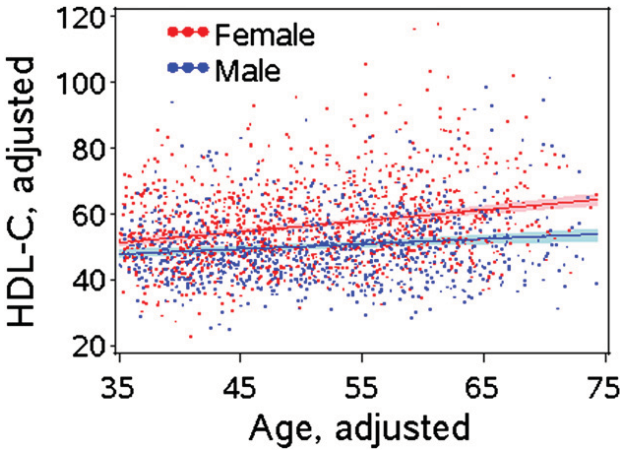

Figure 1 Adjusted HDL-C by adjusted age, Jackson Heart Study Baseline Exam, 2000–2004, n = 2420. HDL-C and age, each adjusted for waist, log2 triglyceride, percent dietary calories as carbohydrates, alcohol use (Y/N), and leisure physical activity above 90th percentile (Y/N).

Although the current report supports other studies that found a positive association of HDL-C with age, especially in women, this finding does not imply that reverse cholesterol transport becomes more effective with age. The contrary situation is more likely: at older ages, HDL particles were less efficient at reverse cholesterol transport; compared with HDL isolated from young subjects, HDL particles from older persons were less able to bring about cholesterol efflux from macrophages, were more susceptible to oxidative damage, and demonstrated impaired activity of paraoxonase, an enzyme that aids in reverse cholesterol transport.[27–30]

A limitation of the current cross-sectional analysis is that it cannot discern whether the association noted between HDL-C and age is a true effect of aging, a survivor effect, or a cohort effect. Perhaps older persons in this population may carry HDL-C at greater levels of serum TG than younger persons because of epigenetic factors relating to differential experiences between birth cohorts. Younger persons in the current study were more likely than older persons to have reported "usual" occupations that are sedentary, but in our final model, having a sedentary occupation was not a significant predictor of HDL-C after control for leisure physical activity and the other predictive covariates. Many of the older persons in the study have retired from their usual occupation, a factor that may have weakened the relation between occupational physical activity and HDL-C in this analysis. In the JHS population, the younger participants are, on average, heavier than the older participants, reflecting the recent obesity epidemic; but the positive association of age with HDL-C in these models was significant even after controlling for waist circumference and TG. It will be

interesting to follow these younger members of the cohort, to learn the trajectory of their HDL-C values with aging, after adjustment for TG and waist measures.

Conclusion

Models of HDL-C using data from a large cross-sectional sample of African Americans found that age was significantly associated with greater HDL-C after controlling for sex, serum triglycerides, waist circumference, dietary carbohydrates, alcohol use, and leisure physical activity. The finding of significant association of age with HDL-C after controlling for triglycerides may indicate an altered relation, with aging, between the HDL particle, cholesterol and TG, a relation that is mediated by cholesterol ester transferase protein and apolipoproteins. Forthcoming analyses will evaluate this relationship in longitudinal data from the JHS, as well as in longitudinal data from cohorts of other races and ethnicities, to establish whether this difference is seen in other populations, and whether the difference appears to be a cohort effect, a survivor effect, or a true effect of aging.

Acknowledgments

The authors thank the participants and staff of the Jackson Heart Study for their continuing dedication to the study.

Financial support

The Jackson Heart Study is conducted by the Jackson State University, the University of Mississippi Medical Center, and Tougaloo College and is supported by National Institutes of Health contracts N01-HC-95170, N01-HC-95171, and N01-HC-95172 from the National Heart, Lung and Blood Institute and the National Institute for Minority Health and Health Disparities. Anne E. Sumner is supported by the intramural program of the National Institute of Diabetes and Digestive and Kidney Diseases.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215.
2. National Center for Health Statistics. 1975. Coronary Heart Disease in Adults, United States: 1960–1962. Series 11, No. 10. Available at: http://www.cdc.gov/nchs/data/series/sr_11/sr11_010.pdf. Accessed December 30, 2010.
3. National Heart Lung and Blood Institute. 2009 October. Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases. Available at: http://www.nhlbi.nih.gov/resources/docs/2009_ChartBook.pdf. Accessed December 28, 2010.
4. Tyroler HA, Hames CG, Krishan I, Heyden S, Cooper G, Cassel JC. Black-white differences in serum lipids and lipoproteins in Evans County. *Prev Med*. 1975;4:541–549.
5. Morrison JA, deGroot I, Kelly KA, et al. Black-white differences in plasma lipids and lipoproteins in adults: the Cincinnati Lipid Research Clinic population study. *Prev Med*. 1979;8:34–39.
6. Crook ED, Clark BL, Bradford ST, et al. From 1960s Evans County Georgia to present-day Jackson, Mississippi: an exploration of the evolution of cardiovascular disease in African Americans. *Am J Med Sci*. 2003;325:307–314.
7. Wallace RB, Colsher PL. Blood lipid distributions in older persons. Prevalence and correlates of hyperlipidemia. *Ann Epidemiol*. 1992;2:15–21.
8. Abbott RD, Garrison RJ, Wilson PW, et al. Joint distribution of lipoprotein cholesterol classes. The Framingham study. *Arteriosclerosis*. 1983;3:260–272.
9. Heitmann BL. The effects of gender and age on associations between blood lipid levels and obesity in Danish men and women aged 35–65 years. *J Clin Epidemiol*. 1992;45:693–702.
10. Schubert CM, Rogers NL, Remsberg KE, et al. Lipids, lipoproteins, lifestyle, adiposity and fat-free mass during middle age: the Fels Longitudinal Study. *Int J Obes Relat Metab Disord*. 2005;30:251–260.
11. Berns MA, de Vries JH, Katan MB. Increase in body fatness as a major determinant of changes in serum total cholesterol and high density lipoprotein cholesterol in young men over a 10-year period. *Am J Epidemiol*. 1989;130:1109–1122.
12. Hubert HB, Eaker ED, Garrison RJ, Castelli WP. Life-style correlates of risk factor change in young adults: an eight-year study of coronary heart disease risk factors in the Framingham offspring. *Am J Epidemiol*. 1987;125:812–831.
13. Anderson KM, Wilson PW, Garrison RJ, Castelli WP. Longitudinal and secular trends in lipoprotein cholesterol measurements in a general population sample. The Framingham Offspring Study. *Atherosclerosis*. 1987;68:59–66.
14. Ingelsson E, Massaro JM, Sutherland P, et al. Contemporary trends in dyslipidemia in the Framingham Heart Study. *Arch Intern Med*. 2009;169:279–286.
15. Zuo H, Shi Z, Hu X, Wu M, Guo Z, Hussain A. Prevalence of metabolic syndrome and factors associated with its components in Chinese adults. *Metabolism*. 2009;58:1102–1108.
16. Abbott RD, Yano K, Hakim AA, et al. Changes in total and high-density lipoprotein cholesterol over 10- and 20-year periods (the Honolulu Heart Program). *Am J Cardiol*. 1998;82:172–178.
17. Morton RE, Zilversmit DB. Inter-relationship of lipids transferred by the lipid-transfer protein isolated from human lipoprotein-deficient plasma. *J Biol Chem*. 1983;258:11751–11757.
18. Taylor HA Jr.. The Jackson Heart Study: an overview. *Ethn Dis*. 2005;15(S6):1–3.
19. Dubbert PM, Carithers T, Ainsworth BE, Taylor HA Jr., Wilson G, Wyatt SB. Physical activity assessment methods in the Jackson Heart Study. *Ethn Dis*. 2005;15(Suppl. 6):56–61.
20. Kim ES, Kwon HS, Ahn CW, et al. Serum uric acid level is associated with metabolic syndrome and microalbuminuria in Korean patients with type 2 diabetes mellitus. *J Diabetes Complications*. 2010. [In Press].
21. Manu P, Tsang J, Napolitano BA, Lesser ML, Correll CU. Predictors of insulin resistance in the obese with metabolic syndrome. *Eur J Intern Med*. 2010;21:409–413.
22. Brunham LR, Kruit JK, Hayden MR, Verchere CB. Cholesterol in beta-cell dysfunction: the emerging connection between HDL cholesterol and type 2 diabetes. *Curr Diab Rep*. 2010;10:55–60.
23. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.
24. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and Hdl Cholesterol decrease with age in older men and women: the Rancho Bernardo Study 1984-1994. *Circulation*. 1997;96:37–43.
25. Truesdale KP, Stevens J, Cai J. Nine-year changes in cardiovascular disease risk factors with weight maintenance in the Atherosclerosis Risk In Communities cohort. *Am J Epidemiol*. 2007;165:890–900.
26. Cheung BM, Li M, Ong KL, et al. High density lipoprotein-cholesterol levels increase with age in American women but not in Hong Kong Chinese women. *Clin Endocrinol (Oxf)*. 2009;70:561–568.

27. Berrougui H, Isabelle M, Cloutier M, Grenier G, Khalil A. Age-related impairment of HDL-mediated cholesterol efflux. *J Lipid Res*. 2007;48: 328–336.
28. Rosenblat M, Karry R, Aviram M. Paraoxonase 1 (PON1) is a more potent antioxidant and stimulant of macrophage cholesterol efflux, when present in HDL than in lipoprotein-deficient serum: relevance to diabetes. *Atherosclerosis*. 2006;187:74–81.
29. Jaouad L, de Guise C, Berrougui H, et al. Age-related decrease in high-density lipoproteins antioxidant activity is due to an alteration in the PON1's free sulfhydryl groups. *Atherosclerosis*. 2006;185:191–200.
30. Girona J, LaVille AE, Sola R, Motta C, Masana L. HDL derived from the different phases of conjugated diene formation reduces membrane fluidity and contributes to a decrease in free cholesterol efflux from human THP-1 macrophages. *Biochim Biophys Acta*. 2003;1633:143–148.