Exploring Avenues for Raising HDL Cholesterol

Benjamin Gordon, MS, ACSM-RCEP, CSCS[1] and J. Larry Durstine, PhD[1]

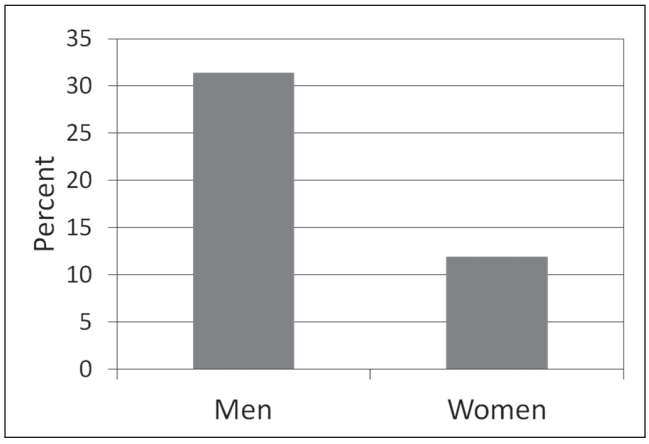
BACKGROUND

Lipids are compounds, including fatty acids, cholesterol, and triglycerides, that play important roles in energy storage, body insulation, cell structure and function, steroid hormone synthesis, and metabolic regulation. Because lipids are not soluble in body fluids, they must combine with apolipoproteins (apo) to form lipoproteins for transport throughout the body. When joined with apolipoproteins, these newly formed lipoproteins take on a spherical shape that surrounds a lipid core containing triglycerides, phospholipids, free cholesterol, and esterified cholesterol. Lipoproteins are categorized by ultracentrifugation according to their gravitational density (53), with as many as 17 different apolipoproteins associated with the four primary lipoprotein classes: chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) (51).

The smallest lipoprotein and arguably most structurally complex is HDL, which is associated with several apolipoproteins; the most prominent are apo A-I and A-II (18). Apo A-1 is the most abundant (18) and is so vital to HDL structure and function that some experts have proposed this apolipoprotein as an independent risk factor for cardiovascular disease (CVD) (42). Being the smallest and densest of all lipoproteins, HDLs have a high protein to lipid ratio and are divided into at least two major subtypes: HDL_2, which contains fewer lipids and is denser than HDL_3, which has more lipid content and is less dense (58). Most HDL_2 originates in the liver (approximately 70%) and are constructed from discoidal lipid particles (51). In the circulation, HDL can gather free cholesterol from peripheral tissues by interacting with the ATP-binding cassette transporter A1 (ABCA1) (52,65). The enzyme lecithin cholesterol acyltransferase (LCAT) converts the cholesterol into cholesteryl ester, which is then moved into the lipoprotein core and is essential for HDL_3 formation. The newly formed spherical HDL_3 has a principle role in gathering cholesterol esters and phospholipids from the circulation. This process of gathering lipids is the primary means for the removal of cholesterol from the body and is known as the reverse cholesterol transport pathway (51). In addition to HDL cholesterol (HDL-C) being the principle means for cholesterol removal, HDL_2 and HDL_3 inhibit LDL cholesterol (LDL-C) oxidation (50), improve endothelial function (47), promote endothelial repair (64), and have antithrombotic and anti-inflammatory properties (13,48). These beneficial properties contributed to HDL-C earning the label of "good" cholesterol.

Present understanding is that HDL-C levels over 40 $mg \cdot dL^{-1}$ are essential for optimal cardiovascular health. An inverse relationship between HDL-C and risk for premature CVD is well established (14,20,59,69). This relationship is especially pertinent to the US population, which has a relatively high percentage of individuals with low HDL-C levels (Figure 1). Interestingly, the prevalence of low HDL-C (i.e., <40 $mg \cdot dL^{-1}$) among men in the United States is nearly

FIGURE 1. Percentage of adults in the United States with low high-density lipoprotein (HDL) cholesterol (< 40 $mg \cdot dL^{-1}$).



Adapted from Carroll MD, Kit BK, Lacher DA. Total and high-density lipoprotein cholesterol in adults: National Health and Nutrition Examination Survey, 2009-2010. NCHS data brief no. 92. Hyattsville, MD: National Center for Health Statistics; 2012.

[1]Department of Exercise Science, University of South Carolina, Columbia, SC 29208

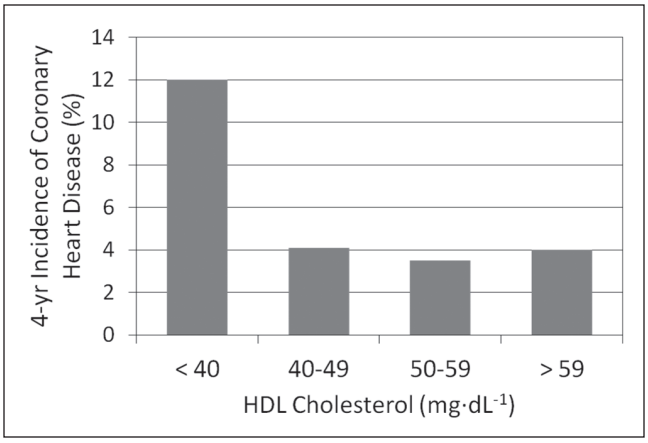
Address for correspondence: J. Larry Durstine, PhD, FACSM, FAACVPR, University of South Carolina, Department of Exercise Science, Blatt PE Center, 1300 Wheat St., Columbia SC, 29208; (803) 777-7680; e-mail: ldurstin@mailbox.sc.edu.

The authors deny any conflicts of interest.

double that of women (55). The discrepancy between genders appears to be an androgen effect and is not related to estrogen or progesterone levels, as previously assumed. Before puberty, males and females have similar HDL-C levels. However, at puberty, male HDL-C levels begin to decline, and this HDL-C decline mirrors the simultaneous rise in endogenous testosterone levels (45,55). Low HDL-C was first identified by the Framingham Heart Study, is now acknowledged as a crucial risk factor for premature CVD, and has gained recognition as being potentially more important than other forms of cholesterol, including LDL-C, for identifying CVD risk (Figure 2) (28). Adding support to this belief, Gordon et al. (27) reviewed epidemiological work, including the Framingham Heart Study, and reported an average of 1 mg·dL^{-1} increase in HDL-C as being associated with a 2 to 3% decreased risk of CVD. Data providing further support for this position come from interventional studies in which CVD risk remained high in spite of substantially lower LDL-C when HDL-C <40 mg·dL^{-1} (3). Concordantly, many scientists and practitioners consider HDL-C as a therapeutic target that is independent of beneficial LDL-C lowering (5). Rubin et al. (56) found that patients with normal levels of LDL-C and low levels of HDL-C and who subsequently increased their HDL-C with gemfibrozil treatment (fibrate drug used to alter lipid levels) can reduce their CVD risk for future events by 22%.

Pharmaceutical interventions for primary and secondary prevention of CVD aimed at raising HDL-C and lowering LDL-C are often recommended (25,66). However, specifically raising HDL-C pharmaceutically has proven difficult because of the complexity of HDL metabolism (51). Fortunately, HDL-C concentrations are influenced by lifestyle intervention, including physical activity and exercise training. HDL-C levels are increased 2 to 8 mg·dL^{-1} when specific exercise training threshold volumes are completed (25,38). Even though these exercise training changes may appear trivial, small HDL-C increases have a dramatic impact on cardiovascular health and CVD risk (5,51).

FIGURE 2. Incidence of coronary heart disease associated with high-density lipoprotein (HDL) cholesterol.



Adapted from Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med. 1977;62(5):707-14.

HDL-C, PHYSICAL ACTIVITY, AND EXERCISE TRAINING

Lifestyle modifications are vital in primary prevention and secondary dyslipidemia management, especially in patients with low HDL-C. Present scientific findings indicate that with lifestyle interventions, such as proper nutrition, physical activity, and regular exercise, many individuals are able to optimize their cholesterol and lipoprotein levels without pharmaceutical intervention (25). A single exercise session and regular exercise participation are known to positively impact triglyceride and HDL-C levels in most individuals and such persons are termed *responders*. However, some individuals experience no HDL-C change regardless of the amount of physical activity and exercise training completed, dubbing them *nonresponders* (7). One estimate is that approximately 19% of all individuals are nonresponders (2). Nonetheless, most exercise training studies report significant HDL-C changes that are positively correlated with the volume of exercise training completed (22). In addition to exercise training, HDL-C changes are related to the individual fitness level (37). Typically, sedentary individuals who complete an exercise training program have larger increases in HDL-C when compared with trained individuals who undergo equivalent increases in exercise training volume (29). The reason for a greater change found in sedentary individuals is likely due to the sedentary group having a greater potential for change in fitness (21).

A single aerobic exercise session of sufficient volume increases HDL-C in most individuals, and some scientists refer to this single exercise session response as *transient* because within several days, the HDL-C returns to pre-exercise values. This HDL-C increase observed with a single exercise session is similar in magnitude to the increase seen with aerobic exercise training, typically resulting in a 4 mg·dL^{-1} (22). This HDL-C rise will peak 24 to 48 h after exercise is completed and can stay elevated for up to 72 h before returning to pre-exercise levels (21). These data support the need for regular physical activity and limiting non-exercise days to a maximum of 2 d. This leaves most individuals needing an exercise frequency of 5 or 6 d·wk^{-1} to achieve the desired exercise volume necessary for optimal HDL-C change (39). The required amount of calories expended during a single exercise session to elicit an increase in HDL-C in a sedentary individual is approximately 350 kcals (16). However, to realize the same HDL-C change in trained individuals will likely require a larger caloric expenditure threshold of 1,000 or more kcals (24). In addition to changes in HDL-C concentrations, the size of HDL-C particles is reportedly increased following a single aerobic exercise session. This finding further supports the belief that a single exercise session can positively alter lipoprotein metabolism (67). However, these changes are temporary or transient, and in order for them to be maintained, regular exercise participation is necessary (21).

For regular aerobic exercise training to increase HDL-C levels, a certain dose threshold of energy expenditure level must be achieved (34). The likelihood of reaching this threshold is increased when training programs last more than 12 wk and include larger exercise training volumes (21,25). While exercise training volume has the strongest and most established correlation, several other factors also contribute to an individual's potential to change HDL-C, including body weight, body composition, and dietary changes (25,34). Large exercise training volumes are often associated with reductions in body weight and body fat percentage that can influence HDL-C levels (25,26). A recent study by Metzner et al. (46) investigated the effects of a 12 wk conventional caloric restriction diet on cardiovascular risk factors, including HDL-C in overweight women. Dietary restriction resulted in significant weight loss that was associated with decreased HDL-C levels.

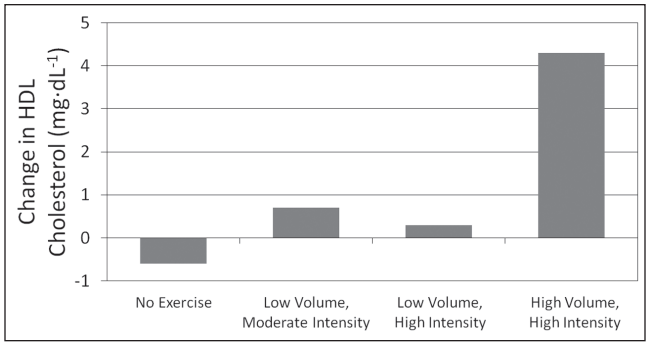
Additionally, a meta-analysis performed by Datillo et al. (17) on the effects of weight loss on serum lipid levels found slight reductions in HDL-C for individuals actively reducing body weight. A second recent meta-analysis by Kelley et al. (35) investigated the combined effects of aerobic exercise and diet on serum lipid levels and found a significant decrease in HDL-C associated with diet and exercise (35). Kelley et al. (35) concluded that the decrease in HDL-C was most likely due to either decreases in total fat intake and/or overall body weight reduction. In support of this concept, Thompson et al. (62) used special diets with supplements to maintain body weight and percentage body fat and reported HDL-C increases of 8 $mg \cdot dL^{-1}$ when body weight did not change after one year of aerobic exercise training. Wood et al. (72) reported that a weight loss program using caloric restriction alone or in combination with exercise training resulted in body weight and body fat decreases with HDL-C increases in all groups. Nonetheless, HDL-C increases seen among the exercise training group were significantly higher than the calorie restricted groups (72). Although the literature supports that large body weight changes and diet restrictions may detract from HDL-C positive change, increased HDL-C is realized through aerobic exercise training.

As opposed to aerobic exercise training, resistance training has limited beneficial effects on lipids and lipoproteins (8,10,12,23,31,33,70), whereas the health benefits reported after resistance exercise training appear to affect non-HDL-C particles. A recent meta-analysis performed by Kelley et al. (33) on 29 studies with a total of 1,329 male and female adult participants provides evidence that regular resistance training can modestly lower total cholesterol and LDL-C with no change in HDL-C. These findings should be interpreted with caution because fewer calories are typically expended during a resistance exercise session versus an aerobic exercise session. Remember that higher calorie expenditures are associated with greater potential of HDL-C change (21). Although resistance training has been viewed as less effective than aerobic training for modifying lipids, the health benefits associated with resistance training are important and should be considered when developing individual exercise prescriptions.

PRESCRIBING EXERCISE TO RAISE HDL-C

Sedentary individuals wanting to increase HDL-C levels through exercise should follow the 2008 *U.S. Physical Activity Guidelines for Americans* (64) in conjunction with the American College of Sports Medicine guidelines (1) and the American Heart Association recommendations (30,61). The 2008 *U.S. Physical Activity Guidelines for Americans* recommends 150 min of moderate intensity or 75 to 150 min of vigorous intensity physical activity per week or a relative mixture (64). In some cases, the 2008 *U.S. Physical Activity Guidelines* for Americans also recommend that 300 min of moderate intensity are needed in order to optimize some physiologic parameters, including lipid levels (64). Typically, individuals with chronic diseases are recommended to use moderate intensity exercise (60 to 85% of heart rate reserve) to avoid any adverse effects of higher intensive exercise (25,41). Generally, HDL-C levels will increase as clients adhere to these exercise guidelines, with a change that is consistent with a dose-response relationship. Supporting this dose-response relationship concept, Kraus et al. (37) reported greater improvements in LDL particle size, HDL-C, and triglyceride levels in dyslipidemic men and women who averaged 20 miles of running and walking per week when compared with individuals who averaged 12 miles of running and walking per week (Figure 3) (37). Exercising at a minimum recommended volume would likely cause modest HDL-C increases (37). However, exercising above the recommended volume can result in greater HDL-C increases in most individuals as well as improving other lipid and lipoproteins levels (25,37).

FIGURE 3. Change in high-density lipoprotein (HDL) cholesterol following 8 mo of exercise training with 3 different programs.



Low volume = caloric expenditure of 14 $kcal \cdot kg^{-1}$ per wk. Low intensity = 40 to 55% peak oxygen uptake. High volume = caloric expenditure of 23 $kcal \cdot kg^{-1}$ per wk. High intensity = 65 to 80% peak oxygen uptake.

Adapted from Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002; 347:1483-92.

Also important to note is that a sedentary person's HDL-C level is likely to decrease with aging (68). The reason for this change is not understood but is likely related to reduced physical activity. For example, if a person is able to maintain higher physical activity and exercise levels as he or she ages, the result is likely a higher HDL-C. In addition, completing daily physical activity or exercise in small segments may provide the same health benefits as one continuous session. For example, three daily 10 min exercise periods or more are as effective at raising HDL-C as is 30 min or more of continuous exercise (34). The mode of aerobic exercise is unlikely to effect the exercise-related change in HDL-C; therefore, the exercise mode should be based on the goals and exercise preferences of the client.

ADJUNCTIVE THERAPY FOR RAISING HDL-C

A substantial amount of evidence exists showing that exercise training is capable of raising HDL-C in most but not all individuals. However, while physical activity and regular exercise training may provide gains of approximately 2 to 8 $mg \cdot dL^{-1}$, these modest gains substantially reduce CVD risk (25). Any increase in HDL-C has the potential to lower the total cholesterol to HDL-C ratio (high ratios are related to increased CVD risk) and reduce CVD risk (51). In addition, many individuals with dyslipidemia are urged to start a low-calorie, low-fat diet (25). While such a diet is beneficial in lowing overall body fat and decreasing LDL-C levels, HDL-C may also be lowered as a result (11). Individuals with low HDL-C levels may benefit from combining exercise with nutritional supplements to raise HDL-C. Omega-3 (ω-3) fatty acids, resveratrol, and niacin are nutritional supplements that have each been shown to improve cardiovascular health (19,40,49,57).

ω-3 fatty acids are polyunsaturated fatty acids commonly found in marine and plant oils. These fats are considered essential in the human diet because the body is unable to synthesize them. Balk et al. (4) in a meta-analysis of randomized controlled trials reported an average increase in HDL-C of 1.6 $mg \cdot dL^{-1}$ with ω-3 fatty acid supplementation. Similar to the HDL-C increases associated with exercise, HDL-C increases found with ω-3 fatty acids supplementation are small but potentially significant. The combined treatment of ω-3 fatty acid supplementation and aerobic exercise has received limited clinical evaluation (60,72). Wooten et al. (73) investigated the effect of three consecutive days of exercise (~65% of $\dot{V}O_2$ max with ~660 kcals expenditure per exercise session) in combination with 42 d of ω-3 fatty acid supplementation (4.55 $g \cdot d^{-1}$) on LDL and HDL particle size, distribution, and concentration. No HDL-C change was found and no clear explanation as to why the exercise treatment had no effect on HDL-C was given.

Potential reasons for no change might include that the exercise treatment was too short and did not meet the necessary exercise volume for change or the subjects already had relatively high HDL-C levels. In contrast, Thomas et al. (60) investigated the combined use of 4 wk of ω-3 fatty acid supplementation (4 $g \cdot d^{-1}$) and a single moderate aerobic exercise session (~60% $\dot{V}O_2$ max and 60 min) on LDL-C and HDL-C subfractions. A synergistic interaction was found between ω-3 fatty acid supplementation and a single aerobic exercise session that resulted in significant HDL-C increases, which was not seen with either ω-3 fatty acid supplementation or a single exercise session alone. A possible synergistic interaction between ω-3 fatty acid and exercise may truly help individuals raise HDL-C and decrease their CVD risk. But to date, no clinical investigations measuring the effects of ω-3 fatty acid supplementation and exercise training on HDL-C concentrations have been completed.

For decades, niacin has been shown to increase HDL-C in clinical trials (60). Niacin, also known as vitamin B3, is an essential nutrient, and when deficiencies occur, the rare disease pellagra can result (32). Niacin naturally occurs in animals and plants and has been used for several decades as a nonsynthetic pharmaceutical means for increasing HDL-C (60). Clinical trials measuring the effect of niacin on lipid and lipoprotein levels use pharmacologic doses that far exceed levels seen in a healthy diet (66). In addition to the increasing HDL-C, niacin has also been shown to decrease LDL-C (15). However, only one peer-reviewed paper has been published regarding the combined effects of niacin and exercise on HDL-C. Koh et al. (36) examined the combined effects of extended release niacin (1,000 $mg \cdot d^{-1}$ for 4 wk) and a single session of moderate intensity exercise (60% heart rate reserve and ~400 kcal of energy expenditure) on lipid and lipoprotein levels. Niacin alone had beneficial effects on HDL-C, while the combined treatment of niacin and exercise had no synergistic effect. Niacin and exercise have been recommended as lifestyle modifications for individuals with dyslipidemia for decades, but research detailing their combined effect is lacking. Perhaps the reason for the lack of scientific investigations into this area is attributed to niacin's potential side effects. In some individuals, "flushing" occurs because of vasodilation occurring in blood vessels near the skin's surface. While this side effect is not dangerous, the associated tingling and burning in the flushed area is distressing to individuals (15).

Resveratrol supplementation for individuals with dyslipidemia is relatively unexplored but may have potential. Produced as a secondary metabolite of some plants (e.g., grape vines), resveratrol is classified as a stilbene (a subcategory of phytochemical) (44). Recent investigations show that resveratrol may decrease CVD risk (6,9,54,71) by decreasing platelet aggregation and increasing HDL-C (6,43). However, to date, no clinical trials investigating the effects of resveratrol on HDL-C levels have been published.

CLINICAL IMPLICATIONS

Having low HDL-C levels is of great clinical importance, and clinical exercise physiologists should understand not only the significance of raising HDL-C in order to reduce CVD risk and/or future cardiac events but should also be

aware of the different interventions and strategies available to raise HDL-C. Twelve to 24 wk of exercise training alone in most individuals (>75%) will increase HDL-C levels within a small range of 2 to 8 mg·dL^{-1} that will dramatically reduce CVD risk (25). To maximize HDL-C improvements with physical activity and exercise, at least 150 to 300 minutes of moderate intensity exercise should be performed weekly (33,34). While resistance exercise training will likely not affect an individual's blood lipid or lipoprotein levels, there are many other potential health benefits gained from resistance exercise training; therefore, resistance exercise should be part of the physical activity and exercise plan for individuals with dyslipidemia. In addition, physical activity and exercise training in most cases may work synergistically with other interventions, such as ω-3 fatty acids, niacin, or resveratrol, to enhance HDL-C change. Finally, despite there being some individuals who either have low blood HDL-C or are nonresponders requiring other intervention methods, physical activity and regular exercise will increase HDL-C levels in most individuals.

Keywords: cholesterol, lipids, dyslipidemia, exercise

REFERENCES

1. American College of Sports Medicine. Guidelines for exercise testing and prescription. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
2. Arnett DK, Baird AE, Barkley RA, Basson CT, Boerwinkle E, Ganesh SK, Herrington DM, Hong Y, Jaquish C, McDermott DA, O'Donnell CJ. Relevance of genetics and genomics for prevention and treatment of cardiovascular disease: a scientific statement from the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation. 2007;115:2878-901.
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-78.
4. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006;189:19-30.
5. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357:1301-10.
6. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006;5:493-506.
7. Bouchard C. Genomic predictors of trainability. Exp Physiol. 2012;97:347-352.
8. Boyden TW, Pamenter RW, Going SB, Lohman TG, Hall MC, Houtkooper LB, Bunt JC, Ritenbaugh C, Aickin M. Resistance exercise training is associated with decreases in serum low-density lipoprotein cholesterol levels in premenopausal women. Arch Intern Med. 1993;153:97-100.
9. Bradamante S, Barenghi L, Villa A. Cardiovascular protective effects of resveratrol. Cardiovasc Drug Rev. 2004;22:169-88.
10. Braith RW, Stewart KJ. Resistance exercise training: its role in the prevention of cardiovascular disease. Circulation. 2006;113:2642-50.
11. Brinton EA, Eisenberg S, Breslow JL. A low-fat diet decreases high density lipoprotein (HDL) cholesterol levels by decreasing HDL apolipoprotein transport rates. J Clin Invest. 1990;85:144-51.
12. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care. 2002;25:2335-41.
13. Cockerill GW, Rye KA, Gamble JR, Vadas MA, Barter PJ. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol. 15:1987-95.
14. Cooney MT, Dudina A, De Bacquer D, Wilhelmsen L, Sans S, Menotti A, De Backer G, Jousilahti P, Keil U, Thomsen T, Whincup P, Graham IM. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. Atherosclerosis. 2009;206:611-6.
15. Crouse JR 3rd. New developments in the use of niacin for treatment of hyperlipidemia: new considerations in the use of an old drug. Coron Artery Dis. 1996;7:321-6.
16. Crouse SF, O'Brien BC, Grandjean PW, Lowe RC, Rohack JJ, Green JS. Effects of training and a single session of exercise on lipids and apolipoproteins in hypercholesterolemic men. J Appl Physiol. 1997;83:2019-28.
17. Datillo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56: 320-8.
18. De Oliveira ESER, Foster D, McGee Harper M, Seidman CE, Smith JD, Breslow JL, Brinton EA. Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. Circulation. 2000;102:2347-52.
19. Demrow HS, Slane PR, Folts JD. Administration of wine and grape juice inhibits in vivo platelet activity and thrombosis in stenosed canine coronary arteries. Circulation. 1195;91:1182-8.
20. Dickson N, Bhula P, Wilson PD. Use of classification of primary obstetric factors in perinatally related mortality surveillance. N Z Med J. 1988;101:228-31.
21. Durstine JL, Grandjean PW, Cox CA, Thompson PD. Lipids, lipoproteins, and exercise. J Cardiopulm Rehabil. 2002;22:385-98.
22. Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD. Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. Sports Med. 2001;31:1033-62.
23. Fahlman MM, Boardley D, Lambert CP, Flynn MG. Effects of endurance training and resistance training on plasma lipoprotein profiles in elderly women. J Gerontol A Biol Sci Med Sci. 2002;57:B54-60.
24. Ferguson MA, Alderson NL, Trost SG, Essig DA, Burke JR, Durstine JL. Effects of four different single exercise sessions on lipids, lipoproteins, and lipoprotein lipase. J Appl Physiol. 1998;85:1169-74.
25. Fletcher B, Berra K, Ades P, Braun LT, Burke LE, Durstine JL, Fair JM, Fletcher GF, Goff D, Hayman LL, Hiatt WR, Miller NH, Krauss R, Kris-Etherton P, Stone N, Wilterdink J, Winston

M. Managing abnormal blood lipids: a collaborative approach. Circulation. 2005;112:3184-209.
26. Foster CJ, Weinsier RL, Birch R, Norris DJ, Bernstein RS, Wang J, Pierson RN, Van Itallie TB. Obesity and serum lipids: an evaluation of the relative contribution of body fat and fat distribution to lipid levels. Int J Obes. 1987;11:151-61.
27. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR Jr., Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989;79:8-15.
28. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med. 1977;62:707-14.
29. Grandjean PW, Crouse SF, Rohack JJ. Influence of cholesterol status on blood lipid and lipoprotein enzyme responses to aerobic exercise. J Appl Physiol. 2000;89:472-80.
30. Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin KA Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med. Sci. Sports Exerc. 2007;39:1423-34.
31. Honkola A, Forsen T, Eriksson J. Resistance training improves the metabolic profile in individuals with type 2 diabetes. Acta Diabetol. 1997;34:245-8.
32. Horwitt MK Niacin-tryptophan relationships in the development of pellagra. Am J Clin Nutr. 1955;3:244-5.
33. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: another look at a meta-analysis using prediction intervals. Prev Med. 2009;49:473-5.
34. Kelley GA, Kelley KS, Roberts S, Haskell W. Efficacy of aerobic exercise and a prudent diet for improving selected lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. BMC Med. 2011;9:74.
35. Kelley GA, Kelley KS, Roberts S, Haskell W. Combined Effects of aerobic exercise and diet on lipids and lipoproteins in overweight and obese adults: a meta-analysis. J Obes. 2012;2012:985902. doi: 10.1155/2012/985902. Epub 2012 Mar 4.
36. Koh Y, Ben-Ezra V, Biggerstaff KD, Nichols DL. Responses of blood lipids and lipoproteins to extended-release niacin and exercise in sedentary postmenopausal women. J Gerontol A Biol Sci Med Sci. 2010;65:924-32.
37. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002;347:1483-92.
38. Kraus WE, Slentz CA. Exercise training, lipid regulation, and insulin action: a tangled web of cause and effect. Obesity (Silver Spring). 2009;17(Suppl 3):S21-6.
39. Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. J Lipid Res. 1982;23:97-104.
40. Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. Mayo Clin Proc. 2008;83:324-32.
41. Liberopoulos EN, Mikhailidis DP, Elisaf MS. Diagnosis and management of the metabolic syndrome in obesity. Obes Rev. 2005;6:283-96.
42. Luc G, Bard JM, Arveiler D, Ferrieres J, Evans A, Amouyel P, Fruchart JC, Ducimetiere P. Lipoprotein (a) as a predictor of coronary heart disease: the PRIME Study. Atherosclerosis. 2002;163:377-84.
43. Magyar K, Halmosi R, Palfi A, Feher G, Czopf L, Fulop A, Battyany I, Sumegi B, Toth K, Szabados E. Cardioprotection by resveratrol: a human clinical trial in patients with stable coronary artery disease. Clin Hemorheol Microcirc. 2012;50:179-87.
44. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727-47.
45. Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. Science. 2005;308:1583-7.
46. Metzner CE, Folberth-Vögele A, Bitterlich N, Lemperle M, Schäfer S, Alteheld B, Stehle P, Siener R. Effect of a conventional energy-restricted modified diet with or without meal replacement on weight loss and cardiometabolic risk profile in overweight women. Nutr Metab (Lond). 2011;8(1):64. doi: 10.1186/1743-7075-8-64.
47. Mineo C, Deguchi H, Griffin JH, Shaul PW. Endothelial and antithrombotic actions of HDL. Circ Res. 2006;98:1352-64.
48. Murphy AJ, Woollard KJ, Hoang A, Mukhamedova N, Stirzaker RA, McCormick SP, Remaley AT, Sviridov D, Chin-Dusting J. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler Thromb Vasc Biol. 2008;28:2071-7.
49. Nardini M, Natella F, Scaccini C. Role of dietary polyphenols in platelet aggregation. A review of the supplementation studies. Platelets. 2007;18:224-43.
50. Negre-Salvayre A, Dousset N, Ferretti G, Bacchetti T, Curatola G, Salvayre R. Antioxidant and cytoprotective properties of high-density lipoproteins in vascular cells. Free Radic Biol Med. 2006;41:1031-40.
51. Ng DS. Treating low HDL ─ from bench to bedside. Clin Biochem. 2004;37:649-59.
52. Oram JF, Lawn RM. ABCA1. The gatekeeper for eliminating excess tissue cholesterol. J Lipid Res. 2001;42:1173-9.
53. Patsch JR, Sailer S, Kostner G, Sandhofer F, Holasek A, Braunsteiner H. Separation of the main lipoprotein density classes from human plasma by rate-zonal ultracentrifugation. J Lipid Res. 1974;15:356-66.
54. Petrovski G, Gurusamy N, Das DK. Resveratrol in cardiovascular health and disease. Ann NY Acad Sci. 2011;1215:22-33.
55. Rossouw JE. Hormones, genetic factors, and gender differences in cardiovascular disease. Cardiovasc Res 2002;53:550-7.
56. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med. 1999;341:410-8.
57. Sakai T, Kamanna VS, Kashyap ML. Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. Arterioscler Thromb Vasc Biol. 2001;21:1783-9.
58. Salonen JT, Salonen R, Seppanen K, Rauramaa R, Tuomilehto J. HDL, HDL2, and HDL3 subfractions, and the risk of acute myocardial infarction. A prospective population study in eastern Finnish men. Circulation. 1991;84:129-39.

59. Tall AR. Plasma high density lipoproteins. Metabolism and relationship to atherogenesis. J Clin Invest. 1990;86:379-84.
60. Thomas TR, Smith BK, Donahue OM, Altena TS, James-Kracke M, Sun GY. Effects of omega-3 fatty acid supplementation and exercise on low-density lipoprotein and high-density lipoprotein subfractions. Metabolism. 2004;53:749-54.
61. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107:3109-16.
62. Thompson PD, Yurgalevitch SM, Flynn MM, Zmuda JM, Spannaus-Martin D, Saritelli A, Bausserman L, Herbert PN. Effect of prolonged exercise training without weight loss on high-density lipoprotein metabolism in overweight men. 1997;Metabolism. 46:217-23.
63. Tso C, Martinic G, Fan WH, Rogers C, Rye KA, Barter PJ. High-density lipoproteins enhance progenitor-mediated endothelium repair in mice. Arterioscler Thromb Vasc Biol. 2006;26:1144-9.
64. US Department of Health and Human Services. 2008 physical activity guidelines for Americans. (U0036). Retrieved from www.health.gov/paguidelines.
65. Wang N, Silver DL, Thiele C, Tall AR. ATP-binding cassette transporter A1 (ABCA1) functions as a cholesterol efflux regulatory protein. J Biol Chem. 2001;276:23742-7.
66. Wierzbicki AS, Mikhailidis DP. Beyond LDL-C—the importance of raising HDL-C. Curr Med Res Opin. 2002;18:36-44.
67. Williams PT, Krauss RM, Vranizan KM, Albers JJ, Wood PD. Effects of weight-loss by exercise and by diet on apolipoproteins A-I and A-II and the particle-size distribution of high-density lipoproteins in men. Metabolism. 1992;41:441-9.
68. Wilson PW, Anderson KM, Harri T, Kannel WB, Castelli WP. Determinants of change in total cholesterol and HDL-C with age: the Framingham Study. J Gerontol. 1993;49:M252-57.
69. Wilson PW, Abbott RD, Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. Arteriosclerosis. 1988;8:737-41.
70. Winett RA, Carpinelli RN. Potential health-related benefits of resistance training. Prev Med. 32001;3:503-13.
71. Wong RH, Howe PR, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. Nutr Metab Cardiovasc Dis. 2011;21:851-6.
72. Wood PD, Strefinick ML, Williams PT, Haskell WL. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. N Engl J Med. 1991;325:461-6.
73. Wooten JS, Biggerstaff KD, Ben-Ezra V. Responses of LDL and HDL particle size and distribution to omega-3 fatty acid supplementation and aerobic exercise. J Appl Physiol. 2009;107:794-800.