Published in final edited form as:

J Mens Health Gend. 2006 ; 3(1): 61–70.

Aerobic exercise and lipids and lipoproteins in men: a meta-analysis of randomized controlled trials

George A. Kelley, DA and Kristi S. Kelley, MEd

School of Medicine, Department of Community Medicine, West Virginia University, Morgantown, WV, USA

Abstract

Background—Aerobic exercise is recommended for improving lipoprotein and lipid levels which at less than their optimal levels are risk factors for cardiovascular disease. Evidence seems lacking for the effectiveness of exercise in reducing these levels, possibly due to small sizes in studies. We concluded a meta-analysis of the studies to examine the effects of aerobic exercise on lipids and lipoproteins in adult men.

Methods—Studies were retrieved via computerized literature searches, cross-referencing from retrieved articles, hand-searching, and expert review of our reference list. Inclusion criteria were randomized controlled trials, aerobic exercise ≥ 8 weeks, adult men ≥ 18 years of age, studies published in journal, dissertation, or master's thesis format, studies published in the English-language between January 1, 1955 and January 1, 2003, and assessment of one or more of the following lipids and lipoproteins: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). All coding was conducted by both authors, independent of each other. Discrepancies were resolved by consensus.

Results—Forty-nine randomized controlled trials representing up to 67 outcomes from 2,990 men (1,741 exercise, 1,249 control) were pooled for analysis. Using random-effects modeling, statistically significant improvements were observed for TC, HDL-C and TG, and a trend for decreases was observed for LDL-C. Changes were equivalent to improvements of 2% for TC and HDL-C, 3% of LDL-C, and 9% for TG.

Conclusions—Aerobic exercise reduces TC and TG and increases HDL-C in men 18 years of age and older.

Keywords

Exercise; Fitness; Males; Cholesterol; Lipids; Lipoproteins; Meta-analysis

Introduction

Cardiovascular disease, the number one cause of mortality among men in the United States (US), was responsible for more than 400,000 deaths in 2002 [1]. In terms of annual expenditures, the total direct and indirect costs associated with cardiovascular disease among men and women in the US have been estimated at \$393.5 billion [2]. Less than optimal lipid and lipoprotein levels are known risk factors for morbidity and mortality from cardiovascular disease [3]. Aerobic exercise has been recommended as a therapeutic lifestyle change for

E-mail: gkelley@hsc.wvu.edu Corresponding author.

Conflict of interest: Neither of the authors have declared a financial interest in a company which manufactures, distributes or is developing drugs of the type discussed (statins) in the article.

improving lipid and lipoprotein levels in adults [3]. However, randomized controlled trials dealing with the effects of aerobic exercise on lipids and lipoproteins in men have led to less than overwhelming results [4–52]. For example, in those trials only the following proportion of outcomes were reported as statistically significant: 15% of total cholesterol (TC), 28% of high-density lipoprotein cholesterol (HDL-C), 21% of low-density lipoprotein cholesterol (LDL-C), and 19% of triglyceride (TG). One reason for the lack of convincing evidence may have to do with the small sample sizes used in those trials. In addition, the reporting of data using the “vote-counting” approach (number of significant versus non-significant results) has been shown to be a less-than-optimal method for synthesizing the literature [53]. Meta-analysis is a quantitative approach in which the results of individual studies are combined to try and reach conclusions regarding the body of evidence on a particular topic. It is especially appropriate when the number of subjects that can be enrolled in most studies is small [54,55]. Although several meta-analyses have been published dealing with the effects of prolonged aerobic exercise on lipids and lipoproteins in adults [56–60] we are not aware of any that have focused exclusively on the effects of aerobic exercise on lipids and lipoproteins in men. Thus, the purpose of this study was to use the meta-analytic approach to examine the effects of aerobic exercise on lipids and lipoproteins in adult men.

Methods

Data sources

Studies for this meta-analysis were retrieved via computerized literature searches (Medline, EMBASE, Sport Discus, Current Contents, Dissertation Abstracts International), cross-referencing from original and review articles, hand searching selected journals, and expert review of our reference list (Dr. William Haskell, personal communication). Keywords used in our searches included exercise, fitness, cholesterol, cardiovascular, lipids, lipoproteins, humans, males.

Study selection

The inclusion criteria for this study were as follows: (1) randomized controlled trials, (2) aerobic exercise training ≥ 8 weeks as the only intervention, (3) adult men ≥ 18 years of age, (4) studies published in English-language journals or as dissertation or master's theses between January 1, 1955 and January 1, 2003, (5) lipids and lipoproteins assessed in the fasting state, (6) data for one or more of the following variables provided: TC, HDL-C, LDL-C, TG. We chose 1955 as the start date because it appeared to be the first time that an exercise training study on this topic had been conducted [61].

Data abstraction

A coding sheet that could hold more than 200 items was developed for this study. The major categories coded were (1) study characteristics, (2) physical characteristics of subjects, (3) training program characteristics, (4) lipid assessment characteristics, (5) primary outcomes, and (6) secondary outcomes. All studies were coded by both authors, independent of each other. Using Cohen's kappa statistic, interrater agreement prior to correcting discrepant items was 0.92.

Statistical analysis

Prior to the start of data analysis, we identified the number of outcomes and subjects that would be available for our primary outcomes analysis and then conducted power estimates for meta-analysis. Using a small effect size of 0.20, a random-effects variance component of 1.0, a two-tailed alpha level of 0.05, and a desired power of 0.80, our power to identify a statistically significant difference was estimated to be 0.99, 0.98, 0.93, and 0.96, respectively, for TC, HDL-

C, LDL-C, and TG. Net changes in lipids and lipoproteins were calculated as the difference (exercise minus control) of the changes (final minus initial) in the mean values from each study. Pooled treatment effects were calculated by assigning weights equal to the inverse of the variance for net changes in lipids and lipoproteins. Ninety-five percent confidence intervals (CIs) were used to establish the statistical significance of our results. A random-effects model was used for all analyses [62,63].

Heterogeneity of lipid and lipoprotein outcomes was examined using the Q statistic [64]. Significant heterogeneity was set at $p \leq 0.10$ versus $p \leq 0.05$ (two-tailed) because the Q statistic suffers from low power [65]. In addition, we used the I^2 statistic to examine the inconsistency of our results [66]. Generally, values of 25%, 50%, and 75% are considered to be indicative of small, moderate, and large amounts of inconsistency [66]. Publication bias was examined using the trim and fill procedure of Duval and Tweedie [67,68]. We also performed cumulative meta-analysis, ranked by year, to determine at what time, if any, lipid and lipoprotein outcomes appeared to stabilize [69]. Secondary outcomes (changes in body weight, body mass index in kg/m^2 , percent body fat, and maximum oxygen consumption in $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) were analyzed using the same methods as those for primary outcomes.

Subgroup analyses

Categorical analyses were conducted using random-effects ANOVA-like models for meta-analysis [65]. All categorizations and analyses were limited by the availability of data and included source of study (journal vs. dissertation or master's thesis), country in which the study was conducted (USA vs. other), race/ethnicity (Black vs. White), use of drugs that could effect lipids and lipoproteins (no vs. some), cigarette smoking (no vs. some), alcohol consumption (no vs. some), previous physical activity (no vs. some), hyperlipidemia (yes vs. no), diabetes (no vs. some), cardiovascular disease (yes vs. no), overweight/obesity (no vs. yes), type of analysis (analysis-by-protocol vs. intention-to-treat), and age (greater than or equal to 40 years versus less than 40 years). We chose 40 years as our older versus younger cutpoint based on the availability of data. A two-tailed alpha level of $p < 0.05$ was used to establish the statistical significance of our results.

Meta-regression

Simple, linear weighted least-squares meta-regression [70] was used to examine the relation between changes in lipids and lipoproteins (TC, HDL-C, LDL-C, TG) and continuous variables [percent dropout, study quality, initial lipid/lipoprotein level, age, initial as well as changes in body weight, body mass index in kg/m^2 , percent body fat, and maximum oxygen consumption in $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, hours after exercise that lipid/lipoprotein assessment took place, length, frequency, intensity, and duration of training, total minutes of training (length $\times$ frequency $\times$ duration), compliance to the exercise protocol, and total minutes of training adjusted for compliance]. We did not conduct any type of multiple regression analyses because of missing data for different variables from different studies and our desire to include the maximum number of endpoints possible for each potential predictor variable. A two-tailed alpha level of $p \leq 0.05$ was used to establish statistical significance of our results.

Other

All statistical tests were two-tailed. Descriptive statistics are reported as mean $\pm$ standard deviation ($\bar{X} \pm \text{SD}$) while primary and secondary outcomes are reported as mean $\pm$ standard error of the mean ($\bar{X} \pm \text{SEM}$). All data were analyzed using SPSS (version 13.0) and Stata (version 8.2).

Results

Study characteristics

Of the 3,750 studies reviewed 59 met our criteria for inclusion [4–52,71–80]. However, we were unable to include 10 studies because of the inability to retrieve necessary lipid and/or lipoprotein data [71–80]. Thus, our percent loss that met our inclusion criteria was approximately 17%, leaving us with a total of 49 studies for analysis [4–52].

Twenty-nine of the studies (59%) were conducted in the US [4–7,9–11,14,15,19,20,22–24,26,28,29,34–38,43–46,49,50,52], three each in Finland [18,30,31], Switzerland [27,40,41], and the United Kingdom [8,39,51], two in Canada [12,33], and one each in Belgium [17], Denmark [21], Germany [48], Israel [32], the Netherlands [13], New Zealand [42], Nigeria [47], Slovenia [25], and Sweden [16].

Forty-seven studies (96%) used a parallel-group design [4–25,27–34,36–52] and two used a crossover design [26,35]. For those studies in which dropout information was discernable, 40 (82%) reported using an analysis-by-protocol approach to analyze their data [4–11,13–26,28,29,31,33–37,39–50,52] and three used the intention-to-treat approach [12,27,51]. Another three studies did not report having any dropouts [30,32,38]. A total of 125 groups (74 exercise, 51 control) representing 2,990 men (1,741 exercise, 1,249 control) and up to 67 outcomes were available for pooling. The number of exercise groups exceeded the number of control groups because some studies included more than one exercise group. In addition, the number of exercise groups (74) exceeded the number of outcomes (67) because some studies included data for one lipid/lipoprotein variable (for example, TC) but not another (for example, HDL-C). For those studies in which data were available, the percentage of subjects that were not available for follow-up assessment ranged from 0% to 57% in the exercise groups ($\bar{X} \pm SD$, $14.2\% \pm 13.8\%$) and 0% to 33% in the control groups ($\bar{X} \pm SD$, $9.2\% \pm 10.2\%$). Study quality ranged from 0 to 4 (median = 2).

Subject characteristics

The baseline characteristics of the subjects are shown in Table 1. For those studies that reported information on race/ethnicity, three reported that all subjects were White [5,12,26], or primarily White (89%) [22], and two reported that all subjects were Black [23,47]. Sixteen studies reported that none of the subjects were taking any type of medication(s) that could affect lipids and/or lipoproteins [7,13,16,18,20–23,27,29,35,39–41,49,50], and four reported that some subjects were taking medication(s) that could affect lipids and/or lipoproteins [8,25,37,51]. For cigarette smoking, 11 studies reported that none of the subjects smoked [4,7,23,25,27,32,34,39,40,45,50] and 14 reported that some of the subjects smoked [8,13,16,18,21,22,24,26,30,31,42,43,49,51]. One study that consisted of two different exercise groups reported that none of the subjects in one of the exercise groups smoked cigarettes and some of the subjects in the second exercise group as well as the control group smoked [41]. For alcohol consumption, two studies reported that none of the subjects consumed alcohol [23,32] and 16 reported that some of the subjects consumed alcohol [6,8,13,16,18,19,21,24,26,27,34,40,42,45,48,49]. Nineteen studies reported that there were no changes in diet during the intervention period [4,7,8,10,11,19,22,26,29,30,32–35,37,38,42,45,49] and another seven reported that there were changes in one or more groups [6,16,21,39,48,50,52]. Thirty-two studies reported that none of the subjects were previously participating in a regular physical activity program [4,6,7,9,13–15,17–23,25–27,29,32,34–36,39–42,44,45,47,49,50,52] and another three reported that some of the subjects were participating in a regular physical activity program [12,16,43]. For comorbidities, three studies reported that all subjects had some type of cardiovascular disease [8,24,51], three reported that all subjects were hyperlipidemic [16,32,48], and five reported

that all subjects were overweight and/or obese [11,15,26,35,50]. None of the studies reported that all subjects had some type of diabetes.

Lipid assessment characteristics

Ten studies assessed lipids and lipoproteins in the supine position [4–6,15,21,26,28,31,40,50] and nine assessed them in the sitting position [9,12,17,30,32,33,35,36,49]. Eight studies reported the assessment of lipids at least twice during each testing period [4,11,21,29,34,35,37,39]. The number of hours that subjects fasted prior to the assessment of lipids and lipoproteins ranged from 10 to 14 ($\bar{X} \pm \text{SD}$, 12 ± 1 hours) for the 41 studies that reported this information [4–9,11,12,14–23,25–27,29–36,37,39–42,44–46,48–50,52]. Post-exercise blood draws occurred 12 to 120 hours ($\bar{X} \pm \text{SD}$, 40 ± 28 hours) after exercise for the 28 studies that reported such [4–7,12,13,16–19,21,23,25,27,28,30–34,37,42,44–50].

Training program characteristics

The most common training modalities were either jogging or a combination of walking and jogging (Table 2). Twenty groups from 12 studies [4,6,10,11,14,19,41,44,45,47,49,49] used jogging as the primary training modality and another 20 groups from 15 studies used a combination of walking and jogging [7,9,12,15,20,27,29,30,34–37,40,46,52]. Another seven groups from four studies used cycling as the primary training modality [23,25,33,38] and four groups from two studies used a combination of walking, jogging, and cycling [5,22]. Two groups from two studies used walking as the primary intervention [39,41] and one group each from the same study used either stair climbing or indoor cross-country skiing [52]. The remaining 19 groups used various combinations of walking, jogging, cycling, swimming, gymnastics, calisthenics, stairclimbing, as well as other unreported activities as the primary types of exercise.

Primary and secondary outcomes

Overall results—Statistically significant reductions were found for TC and TG as well as a trend for statistically significant reductions in LDL-C ($p = 0.08$) (Table 3). In addition, there was a statistically significant increase in HDL-C. The observed changes were equivalent to relative improvements of 2, 9, 2, and 3%, respectively, for TC, TG, LDL-C, and HDL-C. A moderate to large amount of heterogeneity was observed for TC, HDL-C, LDL-C, and TG. No publication bias was observed for any of the lipids and lipoproteins included in our analysis. Cumulative meta-analysis, ranked by year, revealed that (1) decreases in TC have remained stable and statistically significant since 1985, (2) increases in HDL-C have remained stable and statistically significant since 1996, (3) decreases in LDL-C have remained stable and statistically non-significant since 1998, and (4) decreases in TG have remained stable and statistically significant since 1985.

For secondary outcomes, there were statistically significant reductions in body weight, body mass index in kg/m^2 , and percent body fat as well as a statistically significant increase in maximum oxygen consumption in $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Absolute reductions in body composition were equivalent to relative decreases of 1%, 1%, and 4%, respectively, for body weight, body mass index in kg/m^2 , and percent body fat. Changes in maximum oxygen consumption in $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were equivalent to increases of 12%. A small to large amount of heterogeneity was observed for secondary outcomes.

Subgroup analyses—Greater decreases in TC were found for studies from unpublished versus published sources ($Q_b = 4.1$, $p = 0.04$), studies in which some of the subjects consumed alcohol versus those in which none of the subjects consumed alcohol ($Q_b = 6.6$, $p = 0.01$), and studies in which none of the subjects were diabetic versus those in which some of the subjects were diabetic ($Q_b = 4.4$, $p = 0.04$). In addition, greater decreases in TG were found for those

studies that reported that all subjects were hyperlipidemic versus those studies in which all subjects were not hyperlipidemic ($Q_b = 5.4, p = 0.02$). Furthermore, between group increases in HDL-C were greater in older men ($Q_b = 10.4, p = 0.001$). None of the other subgroup analyses were statistically significant or clinically important.

Meta-regression—Greater increases in HDL-C were associated with lower initial levels of HDL-C ($r = 0.45, p < 0.001$), older age ($r = 0.34, p = 0.003$), higher initial body weight ($r = 0.29, p = 0.02$), body mass index in kg/m^2 ($r = 0.29, p = 0.04$), and percent body fat ($r = 0.66, p < 0.001$) as well as lower initial maximum oxygen consumption in $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Greater decreases in LDL-C were associated with higher initial levels of LDL-C ($r = 0.38, p = 0.03$). For TG, greater decreases were associated with higher initial levels of TG ($r = 0.39, p = 0.003$), and greater decreases in percent body fat ($r = 0.39, p = 0.02$). No other statistically significant or clinically important relations were observed for TC, HDL-C, LDL-C, and TG.

Discussion

Our overall results suggest that aerobic exercise improves TC, HDL-C and TG with a trend for statistically significant reductions in LDL-C among men. Although the reductions in TG (9%) were high relative to the improvements for TC (2%) and HDL-C (3%), the small changes observed for the latter two might be important. For example, a reduction of 1% in TC has been shown to reduce the risk for coronary artery disease (CAD) by 2% [81]. For HDL-C, as little as a 1% decrease in HDL-C has been associated with a 2–3% increase in the risk for coronary heart disease (CHD) [82]. Assuming that the reverse is true, the approximate 3% increase observed in our meta-analysis should decrease CHD risk by 6–9%. For TG, previous research has shown that elevated levels are an independent risk factor for CHD [83].

Lowering LDL-C is the primary target of lipid-lowering therapy [3]. Although we did not find a statistically significant reduction in LDL-C as a result of aerobic exercise, there was a trend for statistical significance ($p = 0.08$). The 2% reduction in LDL-C observed in our meta-analysis may also be important because it has been shown that a 1% reduction in LDL-C reduces the risk of major coronary events by approximately 2% [84].

Although our results are encouraging, it appears that aerobic exercise alone might not be sufficient for bringing lipid and lipoprotein levels to recommended levels for many of those with less than optimal levels [3]. Therefore, it would be plausible to suggest that in addition to aerobic exercise [85], additional lifestyle (for example, prudent diet) and/or pharmacologic (for example, statins) interventions are necessary for optimizing lipid and lipoprotein levels in adult men.

The large amount of statistical heterogeneity observed in our results might partly be explained by the results of our subgroup and meta-regression analyses. For TC, greater decreases were found for unpublished versus published studies. These findings are antagonistic to the concept of publication bias where larger and more statistically significant reductions should be found among published versus unpublished studies. Greater decreases in TC were also found for studies in which some of the subjects consumed alcohol as well as studies in which none of the subjects were diabetic. For HDL-C, the statistically significant association between greater increases in HDL-C and initial body composition, especially percent body fat, suggests that those with poorer initial body composition profiles experience greater increases in HDL-C. In addition, the statistically significant association between greater increases in HDL-C with lower initial levels of HDL-C suggests that those with lower levels of HDL-C have the most to gain from an aerobic exercise program. Furthermore, the association and subgroup differences between changes in HDL-C with older age as well as initial maximum oxygen consumption suggests that older people and/or those with lower initial levels of maximum

oxygen consumption experience the greatest increases in HDL-C. For LDL-C, some of the heterogeneity may be explained by the statistically significant association between higher initial levels of LDL-C and greater reductions in LDL-C. Finally, the heterogeneity observed for TG may be partly explained by the association between greater reductions in TG and higher initial levels of TG as well as decreases in percent body fat. Overall, it appears that some of the heterogeneity observed for changes in lipid and lipoprotein levels in adult men may be explained primarily by baseline lipid and lipoprotein levels as well as body composition.

Meta-analysis, like any type of review, is limited by the availability of data. For example, we were unable to conduct any type of multiple regression analysis because of missing data for different variables from different studies and our preference to include the maximum amount of data possible for each analysis. Because of this approach, it is possible that some of the predictor (independent) variables (for example, initial body weight and initial percent body fat) were related to each other. In addition, our subgroup (ANOVA) analyses for changes in TC were limited to two outcomes for the “no” category for alcohol and two outcomes for the category of “some” for diabetes. Finally, our subgroup analyses for drugs that could affect lipids and lipoproteins, cigarette smoking, alcohol consumption, previous physical activity, and diabetes were partitioned according to “no” versus “some” as opposed to “no” versus “yes.”

The fact that we performed a large number of simple regression and ANOVA tests raises the possibility that one or more of our statistically significant findings could be due to nothing more than the play of chance. However, as pointed out by Rothman [86], limiting observations may miss important findings.

Based on our current meta-analytic work, we would suggest that future studies dealing with the effects of aerobic exercise on lipids and lipoproteins in men include complete data on study characteristics (method of randomization, dropout information), subject characteristics (race/ethnicity, drugs that could affect lipids and lipoproteins, cigarette smoking, alcohol consumption, diet, previous physical activity habits), lipid assessment characteristics (instrumentation, timing of post-exercise blood draws), and training program characteristics (compliance to the exercise protocol). The timing of post-exercise blood draws, for example, is vital during lipid and lipoprotein assessment. In addition, future studies should conduct and report power analysis data to ensure that adequate sample sizes are included to answer their research question(s). Furthermore, a major research question that we believe needs to be addressed in future studies is the quantification beyond general recommendations regarding the dose-response relation between aerobic exercise and predicted changes in TC, HDL-C, LDL-C, and TG in men. Answering this research question is critical in determining treatment recommendations on a patient-level basis.

In conclusion, the results of our study suggest that aerobic exercise reduces TC and TG and increases HDL-C in adult men 18 years of age and older.

Acknowledgements

The authors would like to thank William Haskell, PhD, Stanford University, for reviewing our reference list and providing suggestions for the coding of studies.

This study was supported by a grant from the National Institutes of Health-National Heart, Lung and Blood Institute, Award #R01-HL069802 (G.A. Kelley, Principal Investigator).

References

1. Kochanek, KD.; Murphy, SL.; Anderson, RN.; Scott, C. National Vital Statistics Reports. 53. Hyattsville, MD: National Center for Health Statistics; 2004. Deaths: Final data for 2002.

2. American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. Dallas, TX: American Heart Association; 2005.
3. National Cholesterol Education Program, National Heart Lung and Blood Institute, National Institutes of Health. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002;106(25):3143–421. [PubMed: 12485966]
4. Adeniran, SA. The effect of interval and continuous exercise programs on HDL cholesterol, ApoA-I, ApoB and LCAT. University of Kansas; 1982.
5. Adragna NC, Chang JL, Morey MC, Williams RS. Effect of exercise on cation transport in human red cells. *Hypertension* 1985;7:132–9. [PubMed: 2579902]
6. Allison TG, Iammarino RM, Metz KF, Skrinar GS, Kuller LH, Robertson RJ. Failure of exercise to increase high density lipoprotein cholesterol. *J Cardiac Rehabil* 1981;1(4):257–65.
7. Baker TT, Allen D, Lei KY, Willcox KK. Alterations in lipid and protein profiles of plasma lipoproteins in middle-aged men consequent to an aerobic exercise program. *Metabolism* 1986;35:1037–43. [PubMed: 3773721]
8. Ballantyne FC, Clark RS, Simpson HS, Ballantyne D. The effect of moderate physical exercise on the plasma lipoprotein subfractions of male survivors of myocardial infarction. *Circulation* 1982;65(5):913–8. [PubMed: 7074752]
9. Blessing, DL. Dissertation. Louisiana State University; 1983. The effects of two twelve-week training programs on sequential measurements of blood lipids, hormones, cardiovascular function, body composition, and strength in sedentary middle-aged males.
10. Campbell DE. Influence of several physical activities on serum cholesterol concentrations in young men. *J Lipid Res* 1965;6:478–80. [PubMed: 5865375]
11. Campbell DE. Effect of controlled running on serum cholesterol of young adult males of varying morphological constitutions. *Res Q* 1968;39(1):47–53. [PubMed: 5239593]
12. Cunningham DA, Rechnitzer PA, Howard JH, Donner AP. Exercise training of men at retirement: a clinical trial. *J Gerontol* 1987;42:17–23. [PubMed: 3540084]
13. De Geus EJC, Klufit C, De Bart ACW, Van Doornen LJP. Effects of exercise training on plasminogen activator inhibitor activity. *Med Sci Sports Exerc* 1992;24:1210–9. [PubMed: 1435172]
14. Ebisu T. Splitting the distance of endurance running: on cardiovascular endurance and blood lipids. *Jap J Phys Educ* 1985;30–31. 37–43.
15. Hagan RD, Upton SJ, Wong L, Whittam J. The effects of aerobic conditioning and/or caloric restriction in overweight men and women. *Med Sci Sports Exerc* 1986;18(1):87–94. [PubMed: 3457234]
16. Hellenius ML, Faire UD, Berglund B, Hamsten A, Krakau I. Diet and exercise are equally effective in reducing risk for cardiovascular disease. Results of a randomized controlled study in men with slightly to moderate raised cardiovascular risk factors *Atherosclerosis* 1993;103:81–91.
17. Hespel P, Lijnen P, Fagard R, Van Hoof R, Rosseneu M, Amery A. Changes in plasma lipids and apoproteins associated with physical training in middle-aged sedentary men. *Am Heart J* 1988;115(4):786–92. [PubMed: 3354407]
18. Huttunen JK, Lansimies E, Voutilainen E, Ehnholm C, Hietanen E, Penttilä I, et al. Effect of moderate physical exercise on serum lipoproteins: a controlled clinical trial with specific reference to serum high-density lipoproteins. *Circulation* 1979;60:1220–9. [PubMed: 227618]
19. Iltis PW, Thomas TR, Adeniran SB, Aguiar CA, Albers JJ. Different running programs: plasma lipids, apoproteins, and lecithin:cholesterol acyltransferase in middle-aged men. *Ann Sports Med* 1984;2:16–21.
20. Juneau M, Rogers F, De Santos V, Yee M, Evans A, Bohn A, et al. Effectiveness of selfmonitored, home-based, moderate-intensity exercise training in middle-aged men and women. *Am J Cardiol* 1987;60:66–70. [PubMed: 3604945]
21. Kiens B, Jorgensen I, Lewis S, Jensen G, Lithell H, Vessby B, et al. Increased plasma HDL-cholesterol and apo A-1 in sedentary middle-aged men after physical conditioning. *Eur J Clin Invest* 1980;10:203–9. [PubMed: 6783416]

22. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in healthy older men and women: a community- based clinical trial. *J Am Med Assoc* 1991;266:1535–42.
23. Kokkinos PF, Narayan P, Collieran JA, Fletcher RD, Lakshman R, Papadmetriou V. Effects of moderate intensity exercise on serum lipids in African-American men with severe systemic hypertension. *Am J Cardiol* 1998;81:732–5. [PubMed: 9527083]
24. LaRosa JC, Cleary P, Muesing RA, Gorman P, Hellerstein HK, Naughton J. Effect of long-term moderate physical exercise on plasma lipoproteins: The National exercise and heart disease project. *Arch Intern Med* 1982;142:2269–74. [PubMed: 7149870]
25. Lavrencic A, Salobir BG, Keber I. Physical training improves flow-mediated dilation in patients with the polymetabolic syndrome. *Arterioscler Thromb Vasc Biol* 2000;20:551–5. [PubMed: 10671187]
26. Leon AS, Casal D, Jacobs D. Effects of 2,000 kcal per week of walking and stair climbing on physical fitness and risk factors for coronary heart disease. *J Cardiopulm Rehabil* 1996;16:183–92. [PubMed: 8761839]
27. Marti B, Suter E, Riesen WF, Tschopp A, Wanner HU, Gutzwiller F. Effects of long-term, self-monitored exercise on the serum lipoprotein and apolipoprotein profile in middle-aged men. *Atherosclerosis* 1990;81:19–31. [PubMed: 2407251]
28. Milesis CA. Effects of metered physical training on serum lipids of adult men. *J Sports Med* 1974;14:8–14.
29. Milesis CA, Pollock MI, Bah MD, Ayres JJ, Ward A, Linnerud AC. Effects of different durations of physical training on cardiorespiratory function, body composition, and serum lipids. *Res Q* 1976;716–25. [PubMed: 1070744]
30. Rauramaa R, Salonen JT, Kukkonen-Harjula K, Seppanen K, Seppala E, Vapaatalo H, et al. Effects of mild physical exercise on serum lipoproteins and metabolites of arachidonic acid: a controlled randomised trial in middle aged men. *Br Med J (Clin Res Ed)* 1984;288(6417):603–6.
31. Rauramaa R, Vaisanen SB, Kuhanen R, Penttila I, Bouchard C. The RsaI polymorphism in the alpha-fibrinogen gene and response of plasma fibrinogen to physical training—a controlled randomised clinical trial in men. *Thromb Haemost* 2000;83(6):803–6. [PubMed: 10896228]
32. Raz I, Israeli A, Rosenblit H, Kark JD. Effect of moderate exercise on serum lipids in young men with low high density lipoprotein cholesterol. *Arteriosclerosis* 1988;8:245–51. [PubMed: 3370020]
33. Ready EA, Quinney HA. The response of serum lipids and lipoproteins to high intensity endurance training. *Can J Appl Sport Sci* 1982;7:202–8. [PubMed: 7127655]
34. Savage MP, Petratis MM, Thomson WH, Berg K, Smith JL, Sady SP. Exercise training effects on serum lipids of prepubescent boys and adult men. *Med Sci Sports Exerc* 1986;18:197–204. [PubMed: 3702647]
35. Sopko G, Leon AS, Jacobs DR, Foster N, Moy J, Kuba K, et al. The effects of exercise and weight loss on plasma lipids in young obese men. *Metabolism* 1985;34(3):227–36. [PubMed: 3974451]
36. Squires, WG. The effects of exercise and diet modification on HDL cholesterol in middle-aged sedentary males. Texas A&M University; 1979.
37. Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med* 1998;339:12–20. [PubMed: 9647874]
38. Stein RA, Michielli DW, Glantz MD, Sardy H, Cohen A, Goldberg N, et al. Effects of different exercise training intensities on lipoprotein cholesterol fractions in healthy middle-aged men. *Am Heart J* 1990;119:277–83. [PubMed: 2301216]
39. Stensel DJ, Hardman AE, Brooke-Wavell KSF, Vallance D, Jones PRM, Norgan NG, et al. Brisk walking and serum lipoprotein variables in formerly sedentary men aged 42–59 years. *Clin Sci* 1993;85:701–8. [PubMed: 8287662]
40. Suter E, Marti B, Tschopp A, Wanner HU, Wenk C, Gutzwiller F. Effects of self-monitored jogging on physical fitness, blood pressure, and serum lipids: a controlled study in sedentary middle-aged men. *Int J Sports Med* 1990;11:425–32. [PubMed: 2286480]
41. Suter E, Marti B, Gutzwiller F. Jogging or walking-comparison of health effects. *Ann Epidemiol* 1994;4:375–81. [PubMed: 7981845]

42. Sutherland WH, Nye ER, Boulter CP, Shelling A. Physical training plasma lipoproteins and faecal steroid excretion in sedentary men. *Clin Physiol* 1988;8(5):445–52. [PubMed: 3191659]
43. Taylor HL, Buskirk ER, Remington RD. Exercise in controlled trials of the prevention of coronary heart disease. *Fed Proc* 1973;32:1623–7. [PubMed: 4705210]
44. Thomas TR, Adeniran SB, Etheridge GL. Effects of different running programs on VO₂ max, percent fat, and plasma lipids. *Can J Appl Sport Sci* 1984;9:55–62. [PubMed: 6733833]
45. Thomas TR, Adeniran SB, Iltis PW, Aquiar CA, Albers JJ. Effects of interval and continuous running on HDL-cholesterol, apoproteins A-1 and B, and LCAT. *Can J Appl Sport Sci* 1985;10:52–9. [PubMed: 3924425]
46. Tooshi, A. Effect of three different durations of endurance training on serum cholesterol, body composition and other fitness measures. Urbana, IL: University of Illinois; 1970.
47. Toriola AL. Influence of 12-week jogging on body fat and serum lipids. *Br J Sports Med* 1984;18:13–7. [PubMed: 6722418]
48. Wirth A, Diehm C, Hanel W, Welte J, Vogel I. Training-induced changes in serum lipids, fat tolerance, and adipose tissue metabolism in patients with hypertriglyceridemia. *Atherosclerosis* 1985;54:263–71. [PubMed: 3994782]
49. Wood PD, Haskell WL, Blair SN, Williams PT, Krauss RM, Lindgren FT, et al. Increased exercise level and plasma lipoprotein concentrations: a one-year, randomized, controlled study in sedentary, middle-aged men. *Metabolism* 1983;32:31–9. [PubMed: 6848894]
50. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SG, Williams PT, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 1988;319(18):1173–9. [PubMed: 3173455]
51. Wosornu D, Bedford D, Ballantyne D. A comparison of the effects of strength and aerobic exercise training on exercise capacity and lipids after coronary artery bypass surgery. *Eur Heart J* 1996;17:854–63. [PubMed: 8781824]
52. Ziemer, B. The effects of a 12 week training program utilizing various modes of home exercise equipment on cholesterol and triglyceride levels. University of Wisconsin-La-Crosse; 1996.
53. Hedges LV, Olkin I. Vote-counting methods in research synthesis. *Psychol Bull* 1980;88:359–69.
54. Petitti, DB. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. New York, NY: Oxford University Press; 2000.
55. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analysis of randomized controlled trials. *N Engl J Med* 1987;316:450–5. [PubMed: 3807986]
56. Halbert JA, Silagy CA, Finucane P, Withers RT, Hamdorf PA. Exercise training and blood lipids in hyperlipidemic and normolipidemic adults: a meta-analysis of randomized, controlled trials. *Eur J Clin Nutr* 1999;53:514–22. [PubMed: 10452405]
57. Kelley GA, Kelley KS, Tran ZV. Walking, lipids, and lipoproteins: a meta-analysis of randomized controlled trials. *Med Sci Sports Exerc* 2004;36(5):s161.
58. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc* 2001;33(6 Suppl):S502–15. [PubMed: 11427777]
59. Lokey EA, Tran ZV. Effects of exercise training on serum lipid and lipoprotein concentration in women: a meta-analysis. *Int J Sports Med* 1989;10:424–9. [PubMed: 2628361]
60. Tran ZV, Weltman AW, Glass GV, Mood DF. The effects of exercise on blood lipids and lipoproteins: a meta-analysis of studies. *Med Sci Sports Exerc* 1983;15:393–402. [PubMed: 6645868]
61. Mann GV, Teel K, Hayes O, McNally A, Bruno D. Exercise in the disposition of dietary calories: regulation of serum lipoprotein and cholesterol levels in human subjects. *N Engl J Med* 1955;253:349–55. [PubMed: 13244828]
62. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88. [PubMed: 3802833]
63. Hunter JE, Schmidt FL. Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge. *Int J Sel Assess* 2000;8(4):275–92.
64. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101–29.
65. Hedges, LV.; Olkin, I. Statistical methods for meta-analysis. San Diego, CA: Academic Press; 1985.

66. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003;327(7414):557–60. [PubMed: 12958120]
67. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63. [PubMed: 10877304]
68. Duval S, Tweedie R. A nonparametric “trim and fill” method of accounting for publication bias in meta-analysis. *J Am Stat Assoc* 2000;95:89–98.
69. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *J Clin Epidemiol* 1995;48:45–57. [PubMed: 7853047]
70. Lipsey, MW.; Wilson, DB. *Practical meta-analysis*. Thousand Oaks, CA: Sage; 2001.
71. Agren B, Olin C, Castenfors J, Nilsson-Ehle P. Improvements of the lipoprotein profile after coronary bypass surgery: additional effects of an exercise training program. *Eur Heart J* 1989;10(5):451–8. [PubMed: 2788085]
72. Birk, TJ. *The effects of varying exercise intensities and durations on plasma high density lipoprotein-cholesterol, body composition and maximum oxygen consumption*. University of Mississippi; 1981.
73. Blumenthal JA, Emery CF, Madden DJ, George LK, Coleman RE, Riddle MW, et al. Cardiovascular and behavioral effects of aerobic exercise training in healthy older men and women. *J Gerontol* 1989;44:147–57.
74. Fukahori M, Aono H, Saito I, Ikebe T, Ozawa H. Program of exercise training as Total Health Promotion Plan and its evaluation. *J Occup Health* 1999;41:76–82.
75. Katznel LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, Goldberg AP. Effects of weight loss vs. aerobic exercise training on risk factors for coronary disease in healthy, obese, middle-aged and older men. *J Am Med Assoc* 1995;274:1915–21.
76. Mann GV, Garrett HL, Farhi A, Murray H, Billings FT, Shute E, et al. Exercise to prevent coronary heart disease. *Am J Med* 1969;46:12–27. [PubMed: 4951420]
77. Miyai N, Arita M, Miyashita K, Morioka I, Shiraishi T, Nishio I, et al. Antihypertensive effects of aerobic exercise in middle-aged normotensive men with exaggerated blood pressure response to exercise. *Hypertens Res* 2002;25(4):507–14. [PubMed: 12358134]
78. Palank EA, Hargreaves EH. The benefits of walking the golf course: effects of lipoprotein levels and risk ratios. *Phys Sportsmed* 1990;18(10):77–80.
79. Williams PT, Wood PD, Haskell WL, Vranizan KM. The effects of running mileage and duration on plasma lipoprotein levels. *J Am Med Assoc* 1982;247:2674–9.
80. Yeater RA, Ullrich IH, Maxwell LP, Goetsch VL. Coronary risk factors in type II diabetes: response to low-intensity aerobic exercise. *W V Med J* 1990;86(7):287–90. [PubMed: 2368376]
81. Consensus Development Panel. Lowering blood cholesterol to prevent heart disease. *J Am Med Assoc*; Consensus conference; 1985. p. 2080–6.
82. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. *Circulation* 1989;79:8–15. [PubMed: 2642759]
83. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998;81:7B–12B. [PubMed: 9462597]
84. Pedersen TR, Olsson AG, Faergeman O, Kjekshus J, Wedel H, Berg K, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;97(15):1453–60. [PubMed: 9576425]
85. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 1998;30:975–91. [PubMed: 9624661]
86. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1:43–6. [PubMed: 2081237]

Table 1

Baseline characteristics of subjects

Variable	Exercise		Control	
	N	$\bar{X} \pm SD$	Range	N
Age (years)	70	38.7 $\pm$ 11.2	20–63	47
Height (cm)	25	177.6 $\pm$ 3.2	173–185	16
Body weight (kg)	57	80.1 $\pm$ 8.2	63–100	39
BMI (kg/m ²)	42	26.1 $\pm$ 2.3	23–32	29
Body fat (%)	35	22.4 $\pm$ 5.6	12–32	22
VO _{2max} (ml·kg ⁻¹ ·min ⁻¹)	50	39.5 $\pm$ 8.9	21–58	30
TC (mg/dl)	67	209.7 $\pm$ 28.2	144–273	48
Age < 40 years	40	195.5 $\pm$ 24.3	144–251	26
Age $\geq$ 40 years	27	230.8 $\pm$ 18.8	198–273	22
HDL-C (mg/dl)	57	45.4 $\pm$ 6.9	31–60	40
Age < 40 years	31	46.4 $\pm$ 5.5	33–60	21
Age $\geq$ 40 years	26	44.2 $\pm$ 5.9	31–54	19
LDL-C (mg/dl)	39	141.4 $\pm$ 24.4	85–197	27
Age < 40 years	19	126.3 $\pm$ 23.2	85–171	12
Age $\geq$ 40 years	20	155.7 $\pm$ 15.2	135–197	15
TG (mg/dl)	52	136.4 $\pm$ 50.0	77–373	34
Age < 40 years	29	130.5 $\pm$ 46.1	77–239	17
Age $\geq$ 40 years	23	143.8 $\pm$ 54.6	88–373	17

N, total number of groups reporting data for that variable; $\bar{X} \pm SD$, mean $\pm$ standard deviation; Range represents the means for each group from each study; BMI, body mass index; VO_{2max}, maximum oxygen consumption; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Table 2

Training program characteristics

Variable	<i>N</i>	$\bar{X} \pm SD$	Range
Length (weeks)	74	22.3 $\pm$ 22.0	8–156
Frequency (times/week)	69	3.4 $\pm$ 1	2–5
Intensity (% $\text{VO}_{2\text{max}}$)	56	72.7 $\pm$ 13.0	40–91
Duration (minutes/session)	63	36.3 $\pm$ 12.0	8–60
Compliance (%)	30	81.1 $\pm$ 16.1	50–100
Total minutes	41	2,980 $\pm$ 2,871	663–12,960

N, total number of groups reporting data for that variable; $\bar{X} \pm SD$, mean $\pm$ standard deviation; compliance, percentage of exercise sessions attended; total minutes of training calculated as length $\times$ frequency $\times$ duration.

Table 3

Primary and secondary outcomes

Variable	N	$\bar{X} \pm \text{SEM}$	95% CI	Q	p	I^2
Primary outcomes (mg/dl)						
TC (all)	67	-5.1 ± 1.1	-7.2 to -2.9 *	177.2	<0.001 †	62.8
Age < 40 years	40	-6.2 ± 1.5	-9.1 to -3.2 *	95.8	<0.001 †	59.3
Age ≥ 40 years	27	-3.7 ± 1.7	-7.0 to -1.0 *	80.8	<0.001 †	67.8
HDL-C (all)	56	1.3 ± 0.5	0.3 to 2.2 *	294.8	<0.001 †	81.3
Age < 40 years	30	-0.3 ± 0.7	-1.6 to 1.0	139.1	<0.001 †	79.1
Age ≥ 40 years	26	2.6 ± 0.6	1.4 to 3.9 *	112.5	<0.001 †	77.8
LDL-C (all)	38	-3.1 ± 1.8	-6.6 to 0.3	153.6	<0.001 †	75.9
Age < 40 years	20	-3.5 ± 2.8	-9.0 to 2.1	21.3	0.21	20.3
Age ≥ 40 years	18	-2.9 ± 2.3	-7.4 to 1.5	129.2	<0.001 †	85.3
TG (all)	51	-12.2 ± 2.1	-16.3 to -8.2 *	98.2	<0.001 †	49.1
Age < 40 years	29	-9.6 ± 3.0	-15.4 to -3.8 *	42.8	0.04 †	34.5
Age ≥ 40 years	22	-14.7 ± 2.9	-20.3 to -9.1 *	52.0	<0.001 †	59.6
Secondary outcomes						
Body weight (kg)	43	-1.0 ± 0.2	-1.4 to -0.7 *	60.4	0.03 †	30.4
BMI (kg/m ²)	15	-0.3 ± 0.1	-0.6 to -0.1 *	30.2	0.007 †	53.6
Body fat (%)	25	-0.9 ± 0.3	-1.4 to -0.4 *	110.6	<0.001 †	78.3
VO _{2max} (ml·kg ⁻¹ ·min ⁻¹)	42	4.6 ± 0.4	3.9 to 5.4 *	318.6	<0.001 †	87.1

N, total number of groups reporting data in which a treatment effect could be calculated; $\bar{X} \pm \text{SEM}$, mean ± standard error of the mean; CI, confidence interval; Q, heterogeneity value; I^2 , significance value for Q ; I^2 , percentage (%) of inconsistency for study results, calculated from Q statistic; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; BMI, body mass index; VO_{2max}, maximum oxygen consumption.

* Significantly different from zero (0).

† Statistically significant at $p \leq 0.10$.