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Comparison of Aerobic Exercise, Diet or Both on Lipids and Lipoproteins in Adults: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective—Given that previous studies have reached conflicting conclusions regarding the effects of diet (D), aerobic exercise (E) or both (DE) on blood lipid and lipoprotein concentrations in adults, the meta-analytic approach was used to address this issue.

Data Sources—Nine electronic databases, cross-referencing, and expert review.

Study Selection—Randomized controlled trials ≥ 4 weeks that included a D, E, DE and control (C) group in adults ≥ 18 years of age and in which data for one or more of the following were available: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG).

Data Extraction—Dual data extraction by the first two authors.

Statistical Analysis—Random-effects models as well as mixed-effects models for between-group differences.

Results—Seven-hundred and eighty-eight men and women from 6 studies were included. Non-overlapping 95% confidence intervals were observed for D and DE with respect to lowering TC, LDL-C and TG while reductions in E were limited to TG. No significant changes in HDL-C were observed. When compared to E, reductions in TC and LDL-C were greater for D and DE ($p < 0.05$ for all).

Conclusions—Diet, especially DE, are superior to E for improving selected lipids and lipoproteins in adults.

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STATEMENT OF AUTHORSHIP GAK participated in the following: (1) design and coordination of the study, (2) selecting studies, (3) coding studies, (4) data analysis, (5) writing the initial draft of the manuscript. KSK participated in the following: (1) design and coordination of the study, (2) searching for relevant studies, (3) selecting studies, (4) coding studies, (5) reviewing all drafts of the manuscript. SR participated in the design of the study and helped to draft the manuscript. WH participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Keywords

exercise; diet; cholesterol; lipids; lipoproteins; meta-analysis

INTRODUCTION

Cardiovascular disease (CVD) is a major public health problem in the United States (US), affecting approximately 82.6 million men and women ages 20 years and older.¹ Cardiovascular disease is also the leading cause of mortality in the US, accounting for more than 813,000 deaths in 2007.¹ Not surprisingly, the costs associated with CVD are high. For example, the direct and indirect costs for CVD were estimated to be 286.6 billion dollars in 2007.¹ Less than ideal levels of lipid and lipoprotein concentrations, a common problem among US adults, are significant risk factors for morbidity and mortality from CVD.² In 2008, an estimated 98.8 million US men and women had total cholesterol (TC) concentrations of 200 mg/dL or higher. In addition, the prevalence of low-density lipoprotein cholesterol (LDL-C) levels $\geq$ 130 mg/dL was estimated to be 71.3 million among US adults $\geq$ 20 years of age.¹ Furthermore, an estimated 41.8 million US adults have high-density lipoprotein cholesterol (HDL-C) levels $<$ 40 mg/dL.¹

Diet and aerobic exercise, either alone or in combination, are first line interventions for improving lipids and lipoproteins in adults.² Unfortunately, previous randomized controlled trials addressing the effects of all three approaches have reached conflicting conclusions regarding their effects on lipids and lipoproteins.^{3–8} Consequently, the preferred lifestyle treatment strategy for improving lipids and lipoproteins in men and women is not known. Meta-analysis is a method of pooling the results of separate studies. It is a quantitative approach for increasing statistical power of primary end points and subgroups, resolving uncertainty when studies disagree, improving estimates of treatment effects, and answering questions not posed at the start of individual trials.⁹ To the best of the investigative team's knowledge, no meta-analytic work exists on the lipid-modifying effects of randomized controlled trials that included diet, aerobic exercise or both as interventions in adults. Given the former, the purpose of this study was to use the aggregate data meta-analytic approach to determine the effects of diet, aerobic exercise or both on lipids and lipoproteins in adults.

METHODS

Data Sources

Studies were retrieved from a previously developed database that included 1401 unique citations (Figure 1). Citations for the original database were derived from (1) searching 9 electronic databases (PubMed, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, SportDiscus, Dissertation Abstracts International, Physiotherapy Evidence Database (PEDRO), Latin American and Caribbean Health Sciences Database (LILACS), Web of Science), (2) cross-referencing from retrieved studies, and (3) expert review (SR, WH). Major keywords used in the search for potentially eligible studies included “exercise”, “diet”, and “cholesterol”. In accordance with recent guidelines,¹ an example of the search strategy used for one of the electronic databases (EMBASE) is shown in Supplement 1. All electronic searches were conducted using the graphical user interface available for each database. The search strategies used for all databases are available from the corresponding author upon request.

Study Selection

The inclusion criteria for this study were (1) randomized controlled trials with the unit of assignment at the participant level, (2) comparative control (C) group (no intervention, usual care, attention control), (3) three interventions in the same study: diet (D), aerobic exercise (E), combined diet and aerobic exercise (DE) lasting ≥ 4 weeks, (4) adult humans ≥ 18 years of age, (5) studies published as journal articles, dissertations or master's theses, (6) studies published in any language, (7) studies published between January 1, 1955 and May 1, 2009, (8) assessment of one or more of the following lipids and lipoproteins: TC, HDL-C, ratio of TC to HDL-C, non-HDL-C, LDL-C, triglycerides (TG). Any diet considered to improve lipids and lipoproteins in adults (low saturated fat, caloric restriction, etc.) was eligible for inclusion. The year 1955 was chosen as the starting point for the potential inclusion of studies since this appeared to be the first time that an intervention on aerobic exercise and diet had been conducted.¹⁰ Any studies not meeting all of the criteria above were excluded from the study. All studies were selected by the first two authors. They then met and reviewed every selection. Disagreements were resolved by discussion. If agreement could not be reached, the last two authors served as arbitrators.

Data Extraction

Data from study reports were extracted onto electronic coding forms that could hold up to 205 items from each study. All studies were coded by the first two authors, independent of each other. They then met and reviewed each item for agreement. If agreement could not be reached, the last two authors served as adjudicators. Using Cohen's kappa statistic (k),¹¹ the overall agreement rate prior to making corrections was 0.96 for the studies included in the current analysis.

Risk of bias was assessed using the risk of bias assessment tool recommended by the Cochrane Collaboration.¹² Briefly, this assessment tool assesses the risk of bias (low risk, high risk, unclear) across six domains; (1) sequence generation, (2) allocation concealment, (3) blinding of participants, personnel and outcome assessors, (4) incomplete outcome data, (5) selective outcome reporting and (6) sources of bias not included in the previous five domains. For this latter and optional domain, risk of bias was evaluated with respect to whether the participants had been engaged in a regular exercise program, as defined by the authors, prior to study enrollment. Blinding, incomplete outcome data and selective outcome reporting were considered with respect to lipids and lipoproteins, the primary outcomes for the current meta-analysis. Given the nature of lipid assessment, all studies were considered to be at a low risk of bias with respect to blinding. Risk of bias for selective outcome reporting was classified as "low risk" only if the study reported a study protocol identification number.¹³ Risk of bias was assessed by the first two authors. They then met and reviewed every item for agreement. Disagreements were resolved by consensus. Using Cohen's kappa statistic,¹¹ the overall agreement rate prior to correcting discordant results was 0.72.

Statistical Analysis

Calculation of effect sizes from each study—The aggregate data meta-analytic approach was used for this study. *A priori*, the primary outcomes included TC, HDL-C, ratio of TC to HDL-C, non-HDL-C, LDL-C and TG. However, because of a lack of dispersion data, i.e., <5 effect sizes, we were unable to pool data for the ratio of TC to HDL-C and non-HDL-C. Effect sizes for lipid and lipoprotein variables for each group from each study were calculated by subtracting the change score difference in the D, E, and DE groups from the change score difference in the C group. Variances were calculated from the pooled standard deviations of change scores in the intervention and C groups. If change score standard deviations were not available, these were calculated from 95% confidence intervals or pre

and post standard deviation values according to procedures developed by Follmann et al.¹⁴ Each effect size was then weighted by the inverse of its variance. The original metric (milligrams per deciliter) versus some type of standardized metric was used based on the belief that the former is more clinically meaningful.¹⁵

A priori secondary outcomes included changes in body weight, body mass index (BMI) in kg/m², percent body fat, maximum oxygen consumption (VO_{2max} ml·kg⁻¹·min⁻¹), intake of total kilocalories (kcal), fiber and cholesterol as well as the percentage of kcal from protein, total fat, saturated fat, trans-fat and carbohydrates. However, because of a lack of data (<5 effect sizes) the pooling of secondary outcomes was limited to changes in body weight, total kcal, total fat and carbohydrates using the same approach as for primary outcomes.

Pooled effect size estimates for primary and secondary outcomes—All primary and secondary outcomes were pooled using random-effects models, a preferred approach that incorporates heterogeneity into the model.^{16;17} All results were analyzed separately according to group assignment (D, E, DE). Multiple groups within each intervention arm were treated independently as well as after collapsing groups so that only one effect size was provided by each study. Two-tailed 95% confidence intervals that did not cross zero were considered to be statistically significant. Heterogeneity and inconsistency were estimated for all outcomes for each intervention arm using Q and I^2 , respectively.^{18;19} Alpha values ≤ 0.10 were considered statistically significant for Q . For I^2 , values of 25% to <50%, 50% to <75%, and $\geq 75\%$ were considered to represent small, medium, and large amounts of inconsistency.¹⁹

Publication bias was examined using the data imputation approach of Duval and Tweedie²⁰ and with unpublished studies (one dissertation⁴ and one master's thesis⁷) deleted from the analysis. Influence analysis, i.e., examining the overall results by deleting each study from the model once, was also conducted. Cumulative meta-analysis, ranked by year, was used to examine results over time.²¹ Prediction intervals (95%) were calculated in order to estimate ESs if a new trial was conducted.^{22;23}

Between-group (D, E, DE) differences (Q_b) for effect size changes in primary and secondary outcomes were determined using mixed-effects models for meta-analysis. Alpha values ≤ 0.05 were considered statistically significant. In addition, meta-regression was conducted to determine the relationship between effect size changes in lipids and lipoproteins and (1) age, (2) baseline lipid and lipoprotein levels, (3) length of the intervention, (4) changes in body weight, (5) changes in kcal, (6) changes in percent fat intake and (7) changes in percent carbohydrate intake. Non-overlapping 95% confidence intervals for the slope (β_1) were considered statistically significant. Multiple meta-regression was not conducted because of missing data for different variables from different studies. Because of a lack of data (<5 effect sizes), it was not possible to include gender, BMI, percent body fat, VO_{2max} in ml·kg⁻¹·min⁻¹, type of diet, protein, saturated fat, trans-fat, fiber, cholesterol, frequency of training, minutes of exercise per session, intensity of training, minutes per week of training (frequency $\times$ duration), and compliance to the exercise intervention.

Descriptive statistics were generated using Stata (version 11.1),²⁴ reliability statistics using Excel 2007²⁵ and all meta-analytic analyses using Comprehensive Meta-Analysis (version 2.2)²⁶ and the metareg²⁷ and metan²⁸ routines available for use in Stata (version 11.1).²⁴ Data are reported as the mean $\pm$ standard deviation ($\bar{X} \pm SD$), median (Mdn), interquartile range (IQR), percentage (%), 95% confidence intervals (95% CI) and 95% prediction intervals (95% PI).

RESULTS

Study characteristics

Of the 1401 citations reviewed, six studies³⁻⁸ representing 28 groups (7 D, 7 E, 7 DE, 7 C) and up to 788 men and women (207 D, 192 E, 194 DE, 195 C) met all inclusion criteria. A flow diagram that depicts the selection and exclusion of studies is shown in Figure 1 while a general description of each included study is shown in Table 1. The number of intervention and C groups exceeded the number of studies because one study reported data separately for men and women.⁶ Four studies were published in journals,⁵⁻⁸ one as a dissertation⁴ and one as a master's thesis.⁷ All of the studies were published in English.³⁻⁸ One study was conducted in Sweden³ while the remaining five studies were conducted in the United States.⁴⁻⁸ None of the studies used a crossover design. Four studies included a non-intervention C group,^{3;4;6;7} one included an attention C group in which subjects performed stretching exercises^{5;8} while another included a C group in which participants were given a self-help manual as well as advice that encouraged healthy eating, exercise, and weight loss.⁸ With respect to matching, one study used the Efron procedure to balance sample size, HDL-C and LDL-C levels.⁶ For the three groups in which data were available, dropout rates ranged from 0% to 55% in the D groups, 0% to 67% in the E groups, 0% to 64% in the DE groups and 2.5% to 40% in the C groups. The maximum number of participants in which final lipid and lipoprotein data were available ranged from 5 to 49 in the D groups ($\bar{X} \pm SD$, 30 ± 18 , Mdn, 35, IQR, 40), 5 to 47 in the E groups ($\bar{X} \pm SD$, 27 ± 17 , Mdn, 31, IQR, 37), 4 to 48 in the DE groups ($\bar{X} \pm SD$, 28 ± 18 , Mdn, 32, IQR, 37) and 6 to 46 in the C groups ($\bar{X} \pm SD$, 28 ± 17 , Mdn, 31, IQR, 39). All of the studies appeared to use the per-protocol approach in the analysis of their data.³⁻⁸ None of the studies reported justification (power analysis) for their initial sample sizes.³⁻⁸ Four of six studies reported funding for their research.^{3;5;6;8}

Results for risk of bias assessment are shown in Figure 2. All of the studies were considered to be at a low risk of bias with respect to sequence generation and blinding.³⁻⁸ However, the risk of bias for allocation concealment and selective outcome reporting was classified as unclear for all studies.³⁻⁸ The results for incomplete data and exercise prior to participation in the interventions were mixed with two studies considered to be at a high risk of bias for incomplete data^{4;7} and one for engaging regularly in an exercise program prior to taking part in the intervention.³

Participant characteristics

A description of the baseline characteristics of participants is shown in Table 2. Two studies included both men and women,^{6;8} one was limited to men³ while three others were limited to women.^{4;5;7} The within-group age ranges of participants were 20 to 75 years for all groups. For those studies that included women, three consisted of both premenopausal and postmenopausal participants^{5;7;8} while one each included either premenopausal⁴ or postmenopausal⁶ participants. For all studies, it was unclear what the exact race and ethnicity of participants were.³⁻⁸ With respect to medications, one study reported that none of the participants were taking any type of medication that could affect lipid and lipoprotein metabolism.³ One study reported that some participants were taking hormone replacement therapy⁶ while another reported that none were.⁴ Two studies reported that none of the participants smoked cigarettes^{4;5} while two others reported that some did.^{3;7} One study reported that some participants consumed alcohol.³ In relation to physical activity beyond the actual intervention, one study reported that the physical activity level of the control group did not change during the study.³ Three studies reported that all participants were overweight and/or obese^{4;5;8} while the other three reported that some were.^{3;6;7} With respect

to hyperlipidemia, one study reported that all participants were hyperlipidemic⁶ while three others included some participants who were hyperlipidemic.^{3;5;7} Four studies reported that none of the participants had type 1 or 2 diabetes^{3;5;6;8} while another reported that some participants were hypertensive.⁷ Three studies reported that none of the participants had cardiovascular disease prior to enrollment^{3;5;6} while one reported that none of the participants had a history of stroke.⁶ Finally, two studies reported that none of the participants had a history of cancer.^{5;6}

Assessment of primary and secondary outcomes

Five studies reported that participants fasted prior to lipid assessment^{3;4;6-8} with three reporting fasting for at least 12 hours^{4;6;7} and another reporting an overnight fast.³ At least four studies appeared to assess lipids in the morning while^{3;4;6;7} three had participants avoid exercise for at least 12 hours prior to lipid assessment.^{3;4;6} One study reported multiple lipid assessment measures at each testing session.⁶ In relation to the time of year in which lipids were assessed, one study reported lipid assessment between December and May³ while another reported assessment between August and April. Three studies⁴⁻⁶ reported using the Friedewald formula²⁹ for estimating LDL-C.

For bodyweight, four studies reported assessment using a balance beam scale^{4;6-8} with one reporting assessment during two visits.⁶ Nutrient intake was assessed using either a self-reported 3-day food record,⁷ 3-day food record and 24-hour recall,⁵ 7-day food record,³ the mean of 4 weekdays and one weekend from 24-hour dietary recall records via telephone interviews,⁶ or a 3-day food record and Block Food-Frequency Questionnaire.⁸

Intervention characteristics

A description of the intervention characteristics for each study is shown in Table 1. Collectively, intervention length ranged from 10 to 104 weeks ($\bar{X} \pm SD \pm SD$, 39.7 ± 31.8 , Mdn, 24, IQR, 40). For those studies that reported data, the between-study frequency of aerobic exercise training ranged from 2 to 5 times per week ($\bar{X} \pm SD \pm SD$, 3.4 ± 1.1 , Mdn, 3, IQR, 2), intensity from 46.6% to 64.8% of VO_{2max} ($\bar{X} \pm SD \pm SD$, 56.2 ± 10.0 , Mdn, 57, IQR, 17), duration from 45 to 60 minutes per session ($\bar{X} \pm SD \pm SD$, 54.0 ± 6.2 , Mdn, 56, IQR, 10) and total minutes per week of training from 107 to 225 ($\bar{X} \pm SD \pm SD$, 169 ± 40 , Mdn, 180, IQR, 41). Compliance, defined as the percentage of exercise sessions attended, ranged from 29% to 95% ($\bar{X} \pm SD \pm SD$, 66.1 ± 27.8 , Mdn, 70, IQR, 57). The most common exercise performed was walking. Four studies reported that aerobic exercise was both supervised and unsupervised^{3;5;6;8} while two others reported supervised exercise only.^{4;7} For diet, two studies used the Step 1 diet,^{3;5} one used the Step 2 diet,⁶ and one used the 1985 American Heart Association diet.⁷ Another study focused on increasing fiber.⁴ Three studies included a reduction in caloric intake of 800 to 1500 kcals per day.^{4;5;8} None of the studies focused on the reduction of trans fatty acids.

Results for primary and secondary outcomes

Primary outcomes (overall results)—The overall results for lipids and lipoproteins are shown in Table 3 while results from each study are shown in Figures 3–6. For the D group, statistically significant reductions were found for TC, LDL-C and TG but not HDL-C. Changes were equivalent to relative reductions of 4.6%, 2.1% 3.7% and 9.3%, respectively, for TC, HDL-C, LDL-C and TG. Heterogeneity was non-significant as well as nil or small for all lipid and lipoprotein outcomes. Non-overlapping prediction intervals were observed for TC and LDL-C but not HDL-C or TG. When adjusted for publication bias, a statistically significant decrease in HDL-C was found ($\bar{X}$, -1.7 mg/dl, 95% CI, -1.7 to -3.1 mg/dl)

while results remained statistically significant for TG ($\bar{X}$, -1.6 mg/dl, 95% CI, -2.0 to -12.2 mg/dl). No adjustment for publication bias was needed for TC or LDL-C. With each study deleted from the model once, the significance or non-significance of results did not change for TC, HDL-C or LDL-C. However, with the Nieman et al.⁵ study deleted from the model, overlapping confidence intervals were found for TG ($\bar{X}$, -4.5 mg/dl, 95% CI, -10.5 to 1.5 mg/dl). Cumulative meta-analysis demonstrated that results have remained significant since 1998 for TC, LDL-C and TG and non-significant for HDL-C since 1989, the time of the first included study.

For the E group, a statistically significant decrease was found for TG but not TC, HDL-C or LDL-C. Relative to baselines values, changes were equivalent to 0.4%, 2.1%, 1.5% and -5.7%, respectively, for TC, HDL-C, LDL-C and TG. Heterogeneity was non-significant and zero for all lipid and lipoprotein outcomes. Overlapping prediction intervals were observed for all lipid and lipoprotein outcomes. When adjusted for publication bias, results remained statistically significant for TG ($\bar{X}$, -5.3 mg/dl, 95% CIs, -5.3 to -10.9 mg/dl). No adjustment for publication bias was needed for TC, HDL-C or LDL-C. With each study deleted from the model once, the direction of results did not change for TC, HDL-C or LDL-C. However, overlapping 95% CI were found for TG when four studies were independently deleted from the model.^{3;5;6;8} Cumulative meta-analysis demonstrated that results have been significant for TG since 2002 while results have remained non-significant for TC, HDL-C and LDL-C since 1989, the time of the first included study.⁴

Significant improvements were found for TC, LDL-C and TG, but not HDL-C, in the DE groups. Changes were equivalent to reductions of 6.3%, 1.7%, 6.1% and 12.5%, respectively, for TC, HDL-C, LDL-C and TG. A statistically significant and large amount of heterogeneity was observed for LDL-C but not TC, HDL-C or TG. Prediction intervals overlapped for all lipid and lipoprotein outcomes. When adjusted for publication bias, non-overlapping confidence intervals remained for both LDL-C ($\bar{X}$, -8.0 mg/dl, 95% CI, -7.7 to -14.1 mg/dl) and TG ($\bar{X}$, -13.4 mg/dl, 95% CI, -13.2 to -21.2 mg/dl). No adjustments for publication bias were needed for TC or HDL-C. With each study deleted from the model once, results remained significant (non-overlapping 95% CI) for all lipid and lipoprotein outcomes. Cumulative meta-analysis demonstrated that results have remained significant since 1998 for TC, LDL-C and TG while results for HDL-C have remained non-significant since inception of this first study in 1989.⁴

Primary outcomes (between-group differences)—Overall, statistically significant between-group differences in TC were observed between the D, E and DE groups ($Q_b = 24.3$, $p < 0.001$). Two group comparisons revealed that when compared to E, decreases in TC were greater for both the D ($Q_b = 13.6$, $p < 0.001$) and DE ($Q_b = 21.3$, $p < 0.001$) groups. However, no statistically significant difference was found between the D and DE groups ($Q_b = 1.3$, $p = 0.2$). For HDL-C, statistically significant between-group differences were also found between the three groups ($Q_b = 6.7$, $p = 0.04$). Two group comparisons revealed that when compared to E, there were statistically significant decreases in HDL-C for both the D ($Q_b = 5.7$, $p = 0.02$) and DE ($Q_b = 4.3$, $p = 0.04$) groups. However, no statistically significant difference was found between the D and DE groups ($Q_b = 0.06$, $p = 0.8$). Statistically significant differences were also found for changes in LDL-C between the D, E and DE groups ($Q_b = 20.2$, $p < 0.001$). Subgroup analysis showed that decreases in LDL-C were greater in the D versus E group ($Q_b = 8.0$, $p = 0.005$) as well as the DE versus E only group ($Q_b = 13.5$, $p < 0.001$). However, no statistically significant difference was found between the D and DE groups ($Q_b = 1.9$, $p = 0.2$). For TG, no statistically significant differences were found between the three groups ($Q_b = 2.6$, $p = 0.27$). Subgroup analysis resulted in no statistically significant differences between the D and E groups ($Q_b = 0.4$, $p =$

0.5) as well as the D and DE groups ($Q_b = 0.3$, $p = 0.6$). There was a trend ($Q_b = 3.4$, $p = 0.06$) for greater decreases in TG in the DE versus the E groups.

Primary outcomes (meta-regression)—For the D group, simple meta-regression showed that greater reductions in TC were associated with greater decreases in caloric intake (β_1 , 0.03, 95% CI, 0.001 to 0.05). No other statistically significant associations were found between changes in lipids and lipoproteins and potential predictors in the D group. For the E group, greater decreases in TG were associated with higher baseline levels of TG (β_1 , -0.15, 95% CI, -0.24 to -0.07). No other statistically significant associations were found between changes in lipids and lipoproteins and selected predictors in the E group. For the DE group, greater reductions in TC were associated with greater reductions in bodyweight (β_1 , 3.5, 95% CI, 1.2 to 5.8) and caloric intake (β_1 , 0.03, 95% CI, 0.0004 to 0.07). In addition, greater reductions in LDL-C were also associated with greater reductions in bodyweight (β_1 , 2.9, 95% CI, 0.3 to 5.5). For TG, greater reductions were associated with longer intervention periods (β_1 , -0.2, 95% CI, -0.4 to -0.02). No other statistically significant associations were found between changes in lipids and lipoproteins and potential predictors in the DE group.

Secondary outcomes (overall results)—Overall group changes for secondary outcomes are shown in Table 3. As can be seen, statistically significant decreases in body weight, energy intake, and percent fat intake as well as increases in percent carbohydrate were found for the D group. Changes were equivalent to relative reductions of 3.7% 12.4%, and 16.8%, respectively, for body weight, energy and percent fat intake while an increase of 9.3% was found for percent carbohydrate intake. Heterogeneity was found to be large and statistically significant for energy and percent fat intake while overlapping prediction intervals were observed for all secondary outcomes except percent carbohydrate intake. For the E group, there was a statistically significant decrease in body weight but no significant changes for any of the other secondary outcomes. Changes were equivalent to a relative reduction of 1.0% for body weight and increases of 3.0%, 0.6% and 1%, respectively, for energy, percent fat, and percent carbohydrate intake. No statistically significant heterogeneity was observed and all prediction intervals included zero (0). Similar to the D group, statistically significant decreases in body weight, energy and percent fat intake as well as increases in percent carbohydrate were found for the DE group. Changes were equivalent to relative reductions of 4.4% 9.1%, and 18.5%, respectively, for body weight, energy and percent fat intake. An increase of 11.0% was found for percent carbohydrate intake. A large and statistically significant amount of heterogeneity as well as overlapping prediction intervals were found for all secondary outcomes.

DISCUSSION

Therapeutic lifestyle changes in the form of D, E, or DE are recommended as initial strategies for optimizing lipid and lipoprotein levels in adults² as well as cardiovascular risk factor reduction in general.³⁰ Given that the primary purpose of meta-analysis is to reach general conclusions regarding a body of research,³¹ the overall results of the current investigation suggest that D and DE improve TC, LDL-C and TG while E lowers TG only. However, none of the interventions increased HDL-C. In addition, while D and E lowered TG, the significance of results were highly influenced by the results of one study for the D group⁵ and four studies from the E group.^{3,5,6,8}

The significant results observed overall are further supported by the robustness of findings when adjusted for publication bias and when each study was deleted from the model once. Furthermore, improvements in TC, LDL-C and TG have been significant and stable since at least 2002. These findings are important because they help quantify the expected magnitude

of change from D, E and DE interventions, thereby allowing for better treatment decisions in the management of lipid and lipoprotein levels in adults.

In addition to the statistical significance of results, they also appear to be clinically relevant. Based on previous research,³² the decreases observed for TC in the D groups would be equivalent to relative risk reductions of 5% for all cause mortality, 6% for mortality from coronary heart disease and 8% for any coronary heart disease event. For LDL-C, decreases in the D groups would be equivalent to relative risk reductions of 2% for all cause mortality, 4% for mortality from coronary heart disease and 4% for any coronary heart disease event.³² Finally, the observed decreases in TG in the D group would be equivalent to relative risk reductions of 6% for coronary heart disease mortality.³³

The observed decreases in the DE exercise groups also appear to be clinically relevant. For example, the reductions found for TC would be equivalent to relative risk reductions of 6% for all cause mortality, 9% for mortality from coronary heart disease, and 11% for any coronary heart disease event. For LDL-C, the observed reductions would be equivalent to relative risk reductions of 4% for all cause mortality, 6% for mortality from coronary heart disease and 6% for any coronary heart disease event. In addition, decreases in TG would be equivalent to relative risk reductions of 8% for coronary heart disease mortality.³³ Finally, E group changes in TG would equate to a relative risk reduction of 4% for coronary heart disease mortality.³³ Table 4 provides a succinct summary of the aforementioned relative risk reductions for TC, LDL-C and TG across all three groups (D, DE, E).

The benefits of D and DE may be best appreciated if viewed from a population-wide perspective. For example, in 2007, mortality from coronary heart disease was estimated at 406,400 in the United States.¹ Given the observed reductions in LDL-C, currently the primary target of lipid-lowering therapy in adults,² this would be equivalent to avoiding 16,256 deaths from D interventions and 24,385 deaths from DE interventions. The reduction in mortality from DE interventions provides further support for current detailed recommendations regarding such.^{2;30}

While there was a lack of improvement in HDL-C across all three groups, the lack of effect was less in the E versus D and DE groups. However, given what appear to be the superior benefits of D, and especially DE, in improving other lipids and lipoproteins, the incorporation of DE along with nicotinic or fibric acids for increasing HDL-C levels to acceptable levels may be necessary.² For those who cannot lower TC, LDL-C and TG to acceptable levels with DE, the use of HMG CoA reductase inhibitors (statins) may be warranted. Detailed guidelines in the management of lipids and lipoproteins in adults are provided elsewhere.²

The general lack of response of E on lipids and lipoproteins found in the current meta-analysis conflicts with previous meta-analytic work in both men³⁴ and women.³⁵ In the first meta-analysis, statistically significant improvements in TC, HDL-C and TG, as well as a trend for decreases in LDL-C, were found after pooling the results of 49 randomized controlled trials representing 2,990 men.³⁴ A second meta-analysis also reported statistically significant improvements in TC, HDL-C, LDL-C and TG after pooling the results of 41 randomized controlled trials in 1715 women.³⁵ One possible reason for the lack of effect in the current meta-analysis may be the smaller number of studies and participants that were pooled for analysis. Regardless, exercise should almost always be recommended for overall health because of the numerous other benefits that can be derived from such.³⁶

Simple meta-regression analyses resulted in several interesting associations between changes in lipids and lipoproteins and selected predictors. Most notably, decreases in body weight were associated with greater reductions in both TC and LDL-C in the DE groups.

This suggests that weight loss may contribute to improvements in selected lipids and lipoproteins from the DE intervention versus the DE intervention itself. In addition, greater decreases in TC were associated with reductions in total caloric intake in both the D and DE groups. While interesting, this association may have more to do with decreases in caloric intake leading to decreases in body weight and subsequent reductions in TC. The association between changes in TG and higher baseline levels in the E group appears plausible as one might expect greater reductions in lipids and lipoproteins in those with higher initial levels. However, no such associations were found between baseline levels and changes in any other lipids and lipoproteins, including TG, for any of the three groups. Finally, the association between longer intervention periods and greater reductions in TG in the DE groups may have been the result of greater increases in skeletal muscle lipoprotein lipase in longer studies. However, all moderator analyses, including meta-regression results, should be viewed with caution because studies are not randomly assigned to predictors.³⁷ In addition, multiple meta-regression could not be performed because of the small sample sizes and/or missing data for different variables from different studies.

While not the primary outcomes for this meta-analysis, significant decreases in body weight were observed for the D, E and DE groups while decreases in total caloric and percent fat intake, as well as increases in the percentage of carbohydrates consumed, were found for the D and DE groups. The changes in the D and DE groups suggest good adherence to the diet intervention components of the studies while decreases in body weight in the E groups may reflect the increased energy expenditure from aerobic exercise. However, it's important to note that results for secondary outcomes may not be representative of all studies since they were only included if lipid and lipoprotein data were available.

Based on the results of this quantitative review, several recommendations regarding the reporting and conduct of future studies on this topic appear warranted. With respect to reporting, it is suggested that several items that were underreported or not reported at all be reported in future studies. These include (1) a description of the procedures used for allocation concealment, (2) complete data on the number of subjects who dropped out of each group from each study as well as the reasons for such, (3) any adverse events associated with the interventions, (4) information, e.g., clinical trial registry number, to judge whether incomplete outcome reporting occurred, (5) power estimates to justify sample sizes, and (6) data on gender, race and ethnicity, alcohol consumption, BMI, percent body fat, changes in fitness, intake of protein, saturated fat, trans-fat, fiber and cholesterol, time of year in which lipids and lipoproteins were assessed, number of hours subjects fasted and avoided exercise prior to lipid assessment, frequency of training, minutes of exercise per session, intensity of training, minutes per week of training, and compliance to the interventions.

Several suggestions regarding the conduct of future studies appear appropriate. First, since all of the studies appeared to use the per-protocol approach in the analysis of their data, future studies should include both per-protocol and intention-to-treat analyses so that one can determine both the efficacy and effectiveness of the different interventions on lipids and lipoproteins in adults.³⁸ Second, given that non-HDL-C has been shown to be a better predictor of cardiovascular disease morbidity and mortality than LDL-C,³⁹⁻⁴¹ currently the primary target of cholesterol-lowering therapy,² future randomized controlled trials should examine the effects of D, E, and DE on non-HDL-C in adults. Third, since none of the studies examined the use of trans-fats on lipids and lipoproteins, future studies should examine such given their role in the development of cardiovascular disease.⁴²

While the results of the current meta-analysis provide important information in relation to changes in lipids and lipoproteins as a result of D, E and DE, these findings need to be

viewed with respect to the following potential limitations beyond those previously mentioned. First, a moderate to large amount of heterogeneity and inconsistency was observed for some of outcomes. Given these findings and despite the fact that a random-effects model that incorporates heterogeneity into the analysis was used, the generalization of such results may not be appropriate.¹² However, the use of such statistics to determine true heterogeneity and inconsistency is rather arbitrary in nature, and thus, should be viewed with caution.⁴³ A second potential limitation is the fact that the majority of prediction intervals for estimating the expected results of a new trial included zero for all lipid and lipoprotein outcomes. However, these values should not be confused with confidence intervals since prediction intervals are based on a random mean effect while confidence intervals are not.^{22;23} A third potential limitation is the large number of statistical tests that were conducted. As a result, some of the significant findings could have been nothing more than chance findings. Adjustments for multiple tests were not made because of the more severe problems associated with such.^{44;45}

In conclusion, the results of this meta-analysis suggest that D, and especially DE, are superior to E for improving TC, LDL-C and TG in adults. However, a need exists for additional randomized controlled trials on this topic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard abbreviations

D	diet
E	aerobic exercise
DE	diet and aerobic exercise
TC	total cholesterol
HDL-C	high-density lipoprotein cholesterol
TC:HDL-C	ratio of total cholesterol to high-density lipoprotein cholesterol
non-HDL-C	non-high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
TG	triglycerides
CVD	cardiovascular disease

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Figure 1.
Flow diagram for the selection of studies.

Figure 2.
Risk of bias assessment.

Figure 3.
Forest plot for changes in TC (mg/dl).

Figure 4.
Forest plot for changes in HDL-C.

Figure 5.
Forest plot for changes in LDL-C (mg/dl).

Figure 6.
Forest plot for changes in TG (mg/dl).

Table 1

General characteristics of studies.

Study	Country	Subjects (#)	Gender	Age (years)	Interventions	Lipid Assessment
Hellenius et al. (1993) ³	Sweden	D=40 E=39 DE=39 C=39	M	— $\bar{X} \pm SD=46.2 \pm 5$ (range=35–60)	Length (wks): 24 D: <30% F, <10% SF, $\leq 10\%$ PUSF, 10%–15% MUSF, 50%–60% CARBS, 10%–20% PROT, <300 mg/d CHOL (Step 1 diet) E: 2–3× wk, 30–45 min/d, 60%–80% MHR DE: D+E combined	Overnight fast & avoiding exercise for ≥ 24 hr
Hopewell (1989) ⁴	US	D=5 E=5 DE=4 C=6	W	range=20–51	Length (wks): 24 D: 60% CARBS, 20% PROT, 20% FAT, 25 g FIB/d 1200kcal/d E: W, 3× wk, 50 min/d DE: D+E combined	12hr fast & avoiding exercise for ≥ 24 hr
Nieman et al. (2002) ⁵	US	D=26 E=21 DE=22 C=22	W	— $\bar{X} \pm SD=45.6 \pm 10.5$ (range=25–75)	Length (wks): 12 D: 55% CARBS, 30% F, $\leq 10\%$ SF, <300 mg/d of CHOL, 1200–1300 kcal/d. (NCEP Step 1) E: W, 5× wk, 45 min/d, 60%–80% MHR DE: D+E Combined	Unclear
Stefanick et al. (1998) ⁶	US	Women: D=46 E=43 DE=43 C=45 Men: D=49 E=47 DE=48 C=46	W/M	Women: — $\bar{X} \pm SD=56.9 \pm 5.1$ (range=45–64) Men: — $\bar{X} \pm SD=47.8 \pm 8.9$ (range=30–64)	Length (wks): 52 D: <30% F, <7% SF, <200 mg/d CHOL (NCEP Step 2 diet) E: W/J, 3× wk, 60 min/d DE: D+E Combined	Morning after 12–16hr overnight fast & avoiding vigorous physical activity for ≥ 12 hr
Vetro (1990) ⁷	US	D=6 E=6 DE=6 C=6	W	— D $\bar{X} \pm SD=40.5 \pm 6.9$ (range=36–52) E — $\bar{X} \pm SD=33.8 \pm 13.0$ (range=24–59) DE — $\bar{X} \pm SD=36.8 \pm 6.6$ (range=30–49) C — $\bar{X} \pm SD=35.5 \pm 8.5$ (range=24–46)	Length (wks): 10 D: 1985 AHA Diet E: AD, 3× wk, 30 min/d, 70%–85% MHR DE: D+E Combined	12hr overnight fast
Wing et al. (1998) ⁸	US	D=35 E=31 DE=32 C=31	W/M	— D $\bar{X} \pm SD=45 \pm 4.7$ E — $\bar{X} \pm SD=46.4 \pm 4.5$ DE	Length (wks): 104 D: 20% F, 800–1,500 kcal/d, E: W, 5× wk DE: D+E Combined	Fasting

Study	Country	Subjects (#)	Gender	Age (years)	Interventions	Lipid Assessment
				$\bar{X} \pm SD=46.3 \pm 3.8$ C		
				$\bar{X} \pm SD=45.3 \pm 4.9$	range for all groups=40–55	

Notes: Number of subjects limited to those in which final data were available; $\bar{X} \pm SD$, mean $\pm$ standard deviation; wks, weeks; US, United States; D, Diet; E, Aerobic Exercise; DE, Diet + Aerobic Exercise; W, Women; M, Men; F, fat; SF, saturated fat; PUSF, polyunsaturated fat; MUSF, monounsaturated fat; CARBS, carbohydrates; PROT, protein; CHOL, cholesterol; FIB/d, Fiber per day; g, grams; mg/d, milligrams per day; kcal/d, kilocalories per day; NCEP Step 1, National Cholesterol Education Step 1 Diet; NCEP Step 2, National Cholesterol Education Step 2 Diet; AHA, American Heart Association; W, walking; J, jogging; AD, aerobic dance; wk, week; wks, weeks; min/d, minutes per day; MHR, maximum heart rate; hr, hours.

Table 2

Baseline characteristics of participants.

Variable	Studies (#)	Participants (#)	Groups (#)	$\bar{X} \pm SD$	Range	Mdn(IQR)
Diet						
- Age (yrs)	5	204	6	47.0±5.4	41–57	46(3)
- Bodyweight (kg)	5	167	6	81.7±12.1	69–100	80(21)
- TC (mg/dl)	6	207	7	216.8±18.3	189–239	219(34)
- HDL-C (mg/dl)	6	207	7	47.7±6.5	36–54	47(9)
- LDL-C (mg/dl)	6	207	7	142.0±18.7	119–166	138(35)
- TG (mg/dl)	6	207	7	114.1±49.7	49–171	114(96)
- Energy intake (kcal)	5	196	6	1980±297	1537–2421	2008(281)
- Total Fat (%)	4	161	5	32.8±3.5	28–37	33(5)
- Carbohydrates (%)	4	161	5	50.3±6.0	43–57	53(9)
Exercise						
- Age (yrs)	5	193	6	46.1±7.4	34–57	46(2)
- Bodyweight (kg)	4	148	5	81.1±14.3	64–99	84(19)
- TC (mg/dl)	6	192	7	209.6±24.8	180–239	217(50)
- HDL-C (mg/dl)	6	192	7	48.7±7.7	36–60	50(10)
- LDL-C (mg/dl)	6	192	7	136.0±22.6	107–161	138(44)
- TG (mg/dl)	6	192	7	104.9±50.2	57–171	72(95)
- Energy intake (kcal)	5	180	6	1971±278	1619–2421	1919(320)
- Total Fat (%)	5	180	6	33.2±3.4	28–38	34(5)
- Carbohydrates (%)	4	149	5	50.5±5.3	45–57	51(8)
Diet + Exercise						
- Age (yrs)	5	198	6	46.6±6.4	37–57	46(2)
- Bodyweight (kg)	5	155	6	79.7±13.1	68–99	77(22)
- TC (mg/dl)	6	192	7	217±23.6	188–253	214(46)
- HDL-C (mg/dl)	6	194	7	48.3±7.3	36–58	47(10)
- LDL-C (mg/dl)	6	194	7	144±23.1	115–180	142(40)
- TG (mg/dl)	6	194	7	106.1±47	60–171	87(98)
- Energy intake (kcal)	5	182	6	1984±288	1559–2421	2023(251)

Variable	Studies (#)	Participants (#)	Groups (#)	$\bar{X} \pm SD$	Range	Mdn(IQR)
- Total Fat (%)	4	150	5	32.9 $\pm$ 3.6	28–37	33(6)
- Carbohydrates (%)	4	150	5	50.7 $\pm$ 5.6	44–57	53(8)
Control						
- Age (yrs)	5	198	6	46.2 $\pm$ 6.8	36–57	46(3)
- Bodyweight (kg)	4	150	5	80.9 $\pm$ 14.3	63–97	84(21)
- TC (mg/dl)	6	195	7	211.0 $\pm$ 20.6	186–239	200(34)
- HDL-C (mg/dl)	6	195	7	48.3 $\pm$ 9.2	36–63	47(15)
- LDL-C (mg/dl)	6	195	7	138.1 $\pm$ 19.9	117–161	130(40)
- TG (mg/dl)	6	195	7	105.8 $\pm$ 46.9	51–171	108(98)
- Energy intake (kcal)	5	183	6	2032 $\pm$ 288	1669–2421	2022(431)
- Total Fat (%)	5	183	6	33.7 $\pm$ 3.7	28–38	35(6)
- Carbohydrates (%)	4	152	5	50.9 $\pm$ 4.8	46–57	51(8)

Notes #, number; $\bar{X} \pm SD$, mean $\pm$ standard deviation; Mdn(IQR) median and interquartile range; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; To convert TC, HDL-C and LDL-C from mg/dl to mmol, divide by 38.46; To convert TG from mg/dl to mmol, divide by 87.72; To convert from kcal to kilojoules multiply by 4.184; Insufficient data (< 5 groups) reported for body mass index, maximum oxygen consumption (VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$), TC:HDL-C, non-HDL-C, protein, polyunsaturated fat, saturated fat, trans-fat, fiber and cholesterol intake.

Table 3

Changes in primary and secondary outcomes.

Variable	#Studies	# Participants (1±C) ^a	#ES	$\bar{X}$ (95% CI)	Q(p)	I ² (%)	95% PI
Diet							
- TC (mg/dl)	6	402	7	-10.0 (-14.1 to -5.8)*	6.2 (0.41)	2.6	-15.9 to -4.1*
- HDL-C (mg/dl)	6	402	7	-1.0 (-2.1 to 0.2)	5.2 (0.52)	0	-2.4 to 0.5
- LDL-C (mg/dl)	6	402	7	-5.3 (-8.9 to -1.6)*	1.8 (0.94)	0	-10.0 to -0.5*
- TG (mg/dl)	6	402	7	-10.6 (-18.5 to -2.6)*	9.4 (0.16)	35.8	-29.1 to 8.0
- Bodyweight (kg)	4	317	5	-3.0 (-4.2 to -1.8)*	8.0 (0.1)*	50.1	-6.6 to 0.6
- Energy intake (kcal)	5	379	6	-246 (-460 to -32)*	43.8 (<0.001)*	88.6	-983 to 491
- Total fat (%)	4	331	5	-5.5 (-7.9 to -3.0)*	25.4 (<0.001)*	84.3	-14 to 3.1
- Carbohydrates (%)	4	313	5	4.7 (3.8 to 5.7)*	3.6 (0.5)	0	3.2 to 6.2*
Exercise							
- TC (mg/dl)	6	387	7	0.9 (3.2 to 5.0)*	4.0 (0.7)	0	-4.5 to 6.3
- HDL-C (mg/dl)	6	387	7	1.0 (-0.2 to 2.1)	1.2 (0.98)	0	-0.5 to 2.5
- LDL-C (mg/dl)	6	387	7	2.1 (-1.5 to 5.7)	3.5 (0.7)	0	-2.6 to 6.8
- TG (mg/dl)	6	387	7	-6.0 (-11.8 to -0.2)*	3.3 (0.8)	0	-13.5 to 1.6
- Bodyweight (kg)	4	298	5	-0.8 (-1.5 to -0.1)*	3.9 (0.4)	0	-1.9 to 0.4
- Energy intake (kcal)	5	363	6	60 (-6 to 125)	2.3 (0.8)	0	-34 to 153
- Total fat (%)	5	401	6	0.2 (-0.6 to 1.0)	1.7 (0.8)	0	-1.0 to 1.3
- Carbohydrates (%)	4	301	5	0.5 (-0.5 to 1.4)	1.1 (0.9)	0	-1.0 to 2.0
Diet ± Exercise							
- TC (mg/dl)	6	389	7	-13.7 (-19.6 to -7.9)*	10.4 (0.11)	42.2	-28.7 to 1.3
- HDL-C (mg/dl)	6	389	7	-0.8 (-1.9 to 0.4)	4.2 (0.7)	0	-2.3 to 0.8
- LDL-C (mg/dl)	6	389	7	-8.8 (-14.5 to -3.0)*	12.8 (0.05)*	53.2	-24.8 to 7.3
- TG (mg/dl)	6	389	7	-13.3 (-20.1 to -6.6)*	7.4 (0.3)	18.9	-26.8 to 0.1
- Bodyweight (kg)	4	305	5	-3.5 (-5.7 to -1.3)*	18.9 (0.001)*	78.8	-11.3 to 4.3
- Energy intake (kcal)	5	365	6	-181 (-347 to -16)*	25.3 (<0.001)*	80.3	-724 to 362

Variable	#Studies	# Participants	#ES	$\bar{X}$ (95% CI)	Q(p)	I^2 (%)	95% PI
- Total fat (%)	4	332	5	-6.1 (-8.6 to -3.6)*	27.7 (<0.001)*	85.5	-14.9 to 2.7
- Carbohydrates (%)	4	302	5	5.6 (3.4 to 7.8)*	15.4 (0.004)*	74	-1.8 to 13.0

Notes: ES, effect sizes; #, number for which data were available;

a_1 I + C, Intervention + Control participants; $\bar{X}$ (95% CI), mean and 95% confidence interval; Q(p), Cochran's Q statistic for heterogeneity and alpha value; I^2 (%), percent inconsistency statistic; 95% PI, 95% prediction intervals for a new study

* statistically significant; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; To convert TC, HDL-C and LDL-C from mg/dl to mmol, divide by 38.46; To convert TG from mg/dl to mmol, divide by 87.72; To convert from kcals to kilojoules multiply by 4.184; Insufficient data (< 5 ES) reported for body mass index, maximum oxygen consumption ($\text{VO}_{2\text{max}}$ in $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), TC:HDL-C, non-HDL-C, protein, polyunsaturated fat, saturated fat, trans-fat, fiber and cholesterol intake.

Table 4

Relative risk reduction estimates based on changes in TC, LDL-C and TG.

Variable	Diet	Diet + Exercise	Exercise
TC			
- All-Cause Mortality	5%	6%	--
- Coronary Heart Disease Mortality	6%	9%	--
- Any Coronary Heart Disease Event	8%	11%	
LDL-C			
- All-Cause Mortality	2%	4%	--
- Coronary Heart Disease Mortality	4%	6%	--
- Any Coronary Heart Disease Event	4%	6%	--
TG			
- All-Cause Mortality	--	--	--
- Coronary Heart Disease Mortality	6%	8%	4%
- Any Coronary Heart Disease Event	--	--	--

Notes: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; --, not calculated because reductions in selected lipid/lipoprotein were not statistically significant; Relative risk reductions estimated from previous research.^{32;33}