Aerobic exercise and HDL2-C: a meta-analysis of randomized controlled trials
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CRD summary
This review assessed the effects of aerobic exercise on levels of high-density lipoprotein two cholesterol (HDL2-C). The authors concluded that aerobic exercise increases levels of HDL2-C in adults. This was a well-reported review with extensive analyses, but given the variability of the data and often poor quality of the studies, the authors' conclusions should be regarded with some caution.

Authors' objectives
To assess the effects of aerobic exercise on the levels of high-density lipoprotein 2 cholesterol (HDL2-C) in adults.

Searching
MEDLINE, EMBASE, SPORTDiscus, Current Contents and Dissertation Abstracts International were searched from 1st January 1955 to 1st January 2003; the search terms were reported. The authors also checked reference lists from trial and review articles, handsearched a selection of relevant journals (not listed) and contacted a topic expert. Only English language studies published in journals, dissertations or masters theses were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared any aerobic exercise with a no exercise control group were eligible for inclusion. The exercise programmes had to last at least 8 weeks.

The exercise programmes assessed in the review included: walking; cycling; jogging; running; or a combination of walking, jogging, cycling, swimming, skiing, stairclimbing or other miscellaneous activities. Where reported, most studies used supervised exercise programmes but six used supervised and unsupervised sessions and two used only unsupervised programmes. The duration of the exercise programmes ranged from 8 to 104 weeks, with participants taking part in two to seven, 15- to 60-minute sessions per week. In the majority of studies the participants were not taking any medications which could affect their lipid or lipoprotein levels; 2 studies reported that some participants were taking such medications. Only one study reported that participants underwent a change in diet during the study period, whilst another stated that participants were physically active prior to enrolment.

Participants included in the review
Studies that included adults who were at least 18 years old were eligible for inclusion. The review included 8 studies with only male participants, 7 studies with only female participants and 4 studies with both male and female participants. Factors such as co-morbidities that could affect lipid or lipoprotein levels included hyperlipidaemia (1 study), cardiovascular disease (1 study), type 1 diabetes (1 study) and type 2 diabetes (1 study). Three studies reported that all (1 study) or some participants (2 studies) were overweight.

Outcomes assessed in the review
Studies that assessed HDL2-C levels in a fasting state were eligible for inclusion. Of those studies included in the review, three assessed HDL2-C levels in a sitting position and one used a supine position. The participants had to fast for between 10 and 14 hours prior to the retrieval of morning samples and were also asked to avoid exercise for between 14 to 72 hours. Other secondary outcomes included high-density lipoprotein three cholesterol (HDL3-C) levels, high-density lipoprotein cholesterol (HDL-C) levels, body weight, body mass index (BMI), percentage body fat and maximum oxygen consumption.
How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the relevance of studies according to the inclusion criteria. Any disagreements were resolved by consensus.

Assessment of study quality
The validity of the primary studies was assessed using the Jadad scale. Each study was awarded a quality score between 0 (low) and 5 (high). The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data using a standardised form, which was then checked by two reviewers for consistency and accuracy. Any disagreements were resolved by consensus. The reviewers abstracted data according to the following categories: study characteristics; population characteristics (i.e. gender, age, body weight, smoking status, alcohol consumption, co-morbidities etc.); lipid assessment characteristics (i.e. position, number of fasting hours and exercise-free hours prior to measurement etc.); intervention characteristics (i.e. length, frequency, duration, mode etc.); and outcomes.

The net changes in lipoprotein levels were calculated in mg/dL using the difference between the intervention and control groups of the changes (final minus initial) in mean levels. Maximum oxygen consumption levels were recorded as mL/kg per minute. Body fat was recorded as a percentage, body weight in kg, and BMI as kg/m2. Missing data were accounted for in the analysis using the complete case approach.

Methods of synthesis
How were the studies combined?
The studies were combined using a least-squares random-effects model, with overall effect sizes reported with the standard error of the mean and 95% confidence intervals (CIs). CIs were estimated using bias-corrected bootstrapping based on 5,000 iterations; values which did not cross zero were considered to be statistically significant. The findings of the review were also summarised in tables and as a narrative, with the studies grouped according to outcome (i.e. HDL2-C and secondary outcomes). Publication bias was assessed using regression analysis to detect funnel plot asymmetry and by applying Rosenberg’s weighted fail-safe number.

How were differences between studies investigated?
Heterogeneity between studies was assessed using the Q statistic and the I-squared statistic; I-squared values of 25, 50 and 75% were considered to be indicative of low, moderate and high degrees of heterogeneity, respectively. In addition, some difference and similarities between the studies were discussed in the text of the review.

The authors also carried out a random-effects subgroup analysis according to the following: publication source (journal versus other); country of origin (USA versus other); gender (male only versus female only); drugs affecting lipid or lipoprotein levels (taken versus not taken); cigarette smoking (smoking versus not smoking); alcohol consumption (none versus any); menopausal status for women (pre versus post); health status (health versus not); diabetes status (diabetic versus not); and type of exercise programme (supervised versus not).

A simple, weighted and generalised least-squares random-effects meta-regression was performed to assess the relationships between HDL2-C levels and various predefined variables: e.g. initial lipid levels, publication year, study quality, percentage drop-out, age, initial body weight, change in body weight, BMI, percentage body fat, maximum oxygen consumption, number of hours exercise avoided prior to lipid assessment and the length frequency, intensity and duration of intervention, total minutes of intervention (length x frequency x duration) and compliance with intervention. Statistical significance was assessed using randomisation tests of 5,000 iterations; P-values of less than or equal to 0.05 were considered significant.

Sensitivity analyses were also performed to assess the effects of decreases in body composition (body weight, BMI, percentage body fat) in the exercise groups on the levels of HDL2-C. This was achieved by removing any study that reported statistically significant decreases in body composition from the analyses. The effects of study design were assessed by removing one study at a time from the analyses.
Results of the review

Twenty-one studies met the inclusion criteria, but only 19 studies (n=984) were finally included in the analysis; 2 studies failed to provide sufficient data to calculate HDL2-C levels.

Cohen’s kappa for inter-rater agreement between the two data sets was 0.93.

The median score on the Jadad scale was 2 out of 5 points. The scores for the individual studies were not reported. Overall, 0 to 45% of the intervention participants and 0 to 30% of the control participants in the studies did not have follow-up data. For the majority of studies with missing data, data were analysed using an analysis-by-protocol approach.

No statistically significant publication bias (P=0.88) was detected. The authors estimated that 35 studies with null findings would be required to overturn their statistically significant findings for HDL2-C levels.

HDL2-C levels.

HDL2-C levels were significantly decreased in intervention participants in comparison with control participants (19 studies, 20 comparisons; mean change 2.6 +/-0.9 mg/dL, 95% CI: 1.0, 4.4). Fourteen comparisons showed favourable effects for the intervention group, while 6 comparisons showed better results for the control group or showed no difference between the intervention groups; no statistically significant heterogeneity was detected (I-squared 0), and the result remained statistically significant when studies were removed one at a time from the analyses.

Secondary outcomes.

Statistically significant decreases were observed in intervention versus control participants for the following outcomes: body weight (14 studies; mean change -1.4 kg, 95% CI: -2.4, -0.5), BMI (8 studies; mean change -0.3 kg/m2, 95% CI: -0.8, -0.03), body fat (7 studies; mean change -2.3%, 95% CI: -3.4, -0.9) and maximum oxygen consumption (11 studies; mean change 3.5 mL/kg per minute (95% CI: 2.3, 5.2). Beneficial changes in HDL3-C and HDL-C were also observed in intervention participants in comparison with control participants, but these findings were not statistically significant. No statistically significant heterogeneity was detected for any of the analyses, and the results remained statistically significant when studies were removed one at a time from the analyses.

Subgroup analysis.

Increases in HDL2-C were greater for studies carried out in other countries than the USA. No other subgroup analyses showed statistically significant findings.

Sensitivity analysis.

Statistically significant changes in HDL2-C remained despite the removal of studies with significant decreases in body composition.

Regression analysis.

None of the variables assessed showed a statistically significant relationship with HDL2-C levels.

Authors’ conclusions

Aerobic exercise increases levels of HDL2-C in adults.

CRD commentary

This review was based on a clearly defined research question. The review methods were clearly reported with the exception of how studies were selected for inclusion in the review, so it was unclear whether steps were taken to reduce the risk of bias and errors in the study selection process. Appropriate steps were taken to reduce the risk of bias and
errors in the assessment of study quality and the extraction of data. In addition, reasonable attempts were made to locate relevant study data. However, some studies could have been missed by excluding literature not published in English or within a journal, masters thesis or dissertation format; this could also have introduced language and publication bias into the review. Assessments carried out by the authors suggested there was no evidence of publication bias.

The authors carried out extensive analyses of the data and investigated the influences of various potential confounders. However, they entered the control group data twice for one study that had two intervention groups, which will have resulted in the duplication of data. Given the quality and variability of the data presented, the authors' findings and conclusions should be treated with some caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is required to confirm their findings. Future studies should report data on race/ethnicity, alcohol status and co-morbidity status (especially for hyperlipidaemia, cardiovascular disease and obesity) of the participants. Studies should also report details of missing data and, if possible, limit the inclusion of participants to one co-morbidity group (e.g. those with hyperlipidaemia, cardiovascular disease or obesity). Details of how lipoprotein levels are measured are also important.

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