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Effects of Aerobic Exercise on Non-HDL-C in Children and Adolescents: A Meta-Analysis of Randomized Controlled Trials

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Abstract

The authors used the meta-analytic approach to examine the effects of aerobic exercise on non-high-density lipoprotein cholesterol (non-HDL-C) in children and adolescents. Thirteen non-HDL-C outcomes in 404 males and females (221 exercise, 183 control) were available for pooling. Random-effects modeling yielded a non-statistically significant exercise minus control group reduction of 0.61% in non-HDL-C ($\bar{X} \pm \text{SEM}$, -0.7 ± 2.4 mg/dl, 95% CI, -5.4 to 5.0 mg/dl). A statistically significant decrease of 7% was found for percent body fat ($\bar{X} \pm \text{SEM}$, $-2.1 \pm 0.5\%$, 95% CI, -3.0 to -1.2%) as well as an 8% increase in aerobic capacity ($\bar{X} \pm \text{SEM}$, 3.4 ± 1.0 ml·kg⁻¹·min⁻¹, 95% CI, 1.4 to 5.3 ml·kg⁻¹·min⁻¹), both secondary outcomes of the study. It was concluded that aerobic exercise does not reduce non-HDL-C but does improve percent body fat and aerobic capacity in children and adolescents. However, a need exists for additional studies on this topic.

Keywords

exercise; meta-analysis; cholesterol; children; adolescents

INTRODUCTION

It has been suggested that less than optimal lipid and lipoprotein levels in children and adolescents may lead to an increased risk of cardiovascular disease (CVD) in adulthood.¹ This is important since CVD is the leading cause of mortality in the United States, accounting for an estimated 696,947 deaths annually.² One commonly recommended approach for optimizing lipid and lipoprotein levels in children and adolescents is exercise, a low-cost, non-pharmacologic intervention that is available to the vast majority of children and adolescents.¹ While low-density lipoprotein cholesterol (LDL-C) is currently the primary target of lipid-lowering therapy,³ a growing body of evidence suggests that the lowering of non-high-density lipoprotein cholesterol (non-HDL-C), calculated as total cholesterol (TC) minus high-density lipoprotein cholesterol (HDL-C), may be a better predictor of CVD morbidity and mortality in adults.⁴⁻⁸ Given the potential benefits of aerobic exercise and the risk associated with elevated levels of non-HDL-C, we used the meta-analytic approach to examine the effects of aerobic exercise on non-HDL-C in children and adolescents.

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METHODS

The methods used for this meta-analysis have been previously described in detail from a study where non-HDL-C was not included as an outcome and in which studies only published up to January 1, 2005 were included.⁹ Briefly, data sources for our current meta-analysis encompassed 52 years (1955 through 2007) and included five electronic databases (PubMed, EMBASE, Sport Discus, Cochrane Central Register of Controlled Trials, Dissertation Abstracts International), hand searching, and cross referencing from retrieved articles. Studies were included if they were (1) published in English-language journals or as Master's Theses or Dissertations, (2) randomized controlled trials in children and adolescents 5-19 years of age, (3) consisted of at least 4 weeks of aerobic exercise with no diet intervention, and (4) included measures of TC and HDL-C so that non-HDL-C could be calculated.

All studies were coded for (1) study characteristics (for example, year of publication), (2) subject characteristics (for example, age), (3) lipid assessment characteristics (for example, number of hours fasted), (4) training program characteristics (for example, length of training), (5) changes in TC and HDL-C so that non-HDL-C could be calculated, and (6) changes in body weight, percent body fat, and maximum oxygen consumption ($\text{VO}_{2\text{max}}$ in $\text{ml}/\text{kg}^{-1}\text{min}^{-1}$). All studies were coded by both authors, independent of each other. Study quality was examined using a previously validated and reliable 5-point scale that ranges from a low of 0 to a high of 5 with higher scores representing greater study quality.¹⁰ However, all quality rating scales need to be interpreted with caution since no gold standard currently exists.¹¹

The primary outcome in this study was changes in non-HDL-C while secondary outcomes included changes in TC, HDL-C, body weight, percent body fat, and $\text{VO}_{2\text{max}}$ in $\text{ml}/\text{kg}^{-1}\text{min}^{-1}$. For both our primary and secondary outcomes, we calculated the treatment effect by subtracting the change score difference in the exercise group from the change score difference in the control group for each outcome from each study. The treatment effect variance for each outcome from each study was calculated by pooling the change score dispersion statistics from the exercise and control groups. Treatment effects weighted by the inverse of the variance from each study were then pooled using a random-effects model that incorporates between-study heterogeneity into the analysis. Two-tailed 95% confidence intervals (CIs) that did not cross zero (0) were considered to be statistically significant. Heterogeneity (Q and I^2) was examined using a fixed effects model.^{12, 13} An alpha value for Q of $p \leq 0.10$ was considered to be indicative of statistically significant heterogeneity while I^2 values of 25%, 50% and 75% were considered to be representative of low, moderate, and high amounts of heterogeneity.^{12, 13}

Publication bias was examined using the regression approach of Egger et al. and an alpha level of $p \leq 0.05$ to determine if statistically significant publication bias existed.¹⁴

Sensitivity analyses for treatment effect changes in non-HDL-C were performed by deleting each study from the model once. In addition, we performed cumulative meta-analysis, ranked by year, in order to examine our results over time.¹⁵ Based on the availability of data, we further examined non-HDL-C when limited to (1) studies published in journals, (2) males, (3) no reported use of drugs that could affect lipid and lipoprotein levels, (4) no reported cigarette smoking, (5) no reported changes in diet that could affect lipid and lipoprotein levels, (6) no prior participation in a structured exercise program, (7) subjects with type 1 diabetes, (8) subjects who were overweight and/or obese, (9) studies that reported the assessment of lipids and lipoproteins at least 24 hours after the last exercise session, and (10) studies in which the groups had initial TC levels > 170 mg/dl and HDL-C

levels ≤ 60 mg/dl. Finally, we used meta-regression to examine the relationship between changes in non-HDL-C and initial non-HDL-C, year of publication, study quality, percent dropout, age, changes in body weight, body fat, and $\text{VO}_{2\text{max}}$ in $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, length, frequency, intensity, duration and the average number of minutes of training per week. Because of the large number of sensitivity analyses conducted, we used 99% versus 95% confidence intervals to establish the statistical significance of our findings.

RESULTS

Study Characteristics

Of the 235 studies reviewed, 14 met our inclusion criteria.¹⁶⁻²⁹ However, lipid data that was assessed but not reported were not available for two studies.^{28, 30} Thus, a total of 12 randomized controlled trials were included in our meta-analysis.¹⁶⁻²⁷ Nine of 12 studies (75%) were conducted in the United States,¹⁶⁻²⁴ two were conducted in Greece^{25, 26} and one was conducted in the United Kingdom.²⁷ This included a total of 25 groups (13 exercise and 12 control), representing initial and final assessment in 404 males and females (221 exercise and 183 control). The number of exercise groups exceeded the number of control groups because one study included more than one exercise group.²⁴ All of the studies appeared to use an analysis-by-protocol approach for data analysis.¹⁶⁻²⁷ The percentage of subjects that was not available for follow-up assessment ranged from 0% to 28% in exercise groups ($\bar{X} \pm \text{SD}$, $8.3 \pm 9.5\%$) and 0% to 20% in the control groups ($\bar{X} \pm \text{SD}$, $9.1 \pm 7.9\%$). Study quality ranged from 1 to 2 (median = 2).

Subject Characteristics

Initial characteristics of the subjects are shown in Table 1. Five studies were limited to males^{20, 23-26} while one was limited to females.²⁷ The remaining six studies included both males and females.^{16-19, 21, 22} We were unable to determine the exact number of males and females (separately) that were available for follow-up assessment because of missing data from three studies.^{16, 18, 21} For race/ethnicity, one study each reported that subjects were either White,²³ White, Black, or Asian,²¹ or White, Asian or Hispanic.²⁰ For medication usage, five studies reported that none of the subjects were taking any types of drugs that could affect lipid and lipoprotein metabolism.^{19, 20, 23, 25, 26} One study reported that none of the subjects consumed alcohol²⁰ while four reported that none of the subjects were current cigarette smokers.^{16, 19, 20, 24} Eight of the 12 studies (67%) reported that none of the subjects were currently participating in a regular structured exercise program.^{16, 17, 19-21, 24-26} Eight studies also reported information on diet during the study so as to ensure that the subjects' diets did not change during the intervention.^{16-19, 21-24} Two studies reported that all subjects had type 1 diabetes^{18, 19} while two others reported that all subjects were overweight and/or obese.^{21, 22} None of the studies reported that all subjects were hyperlipidemic.

Lipid Assessment Characteristics

The assessment of lipids and lipoproteins took place in the morning after an overnight fast ranging from 8 to 12 hours ($\bar{X} \pm \text{SD}$, 11.4 ± 0.9 hours). The number of hours that exercise was avoided prior to the assessment of lipids and lipoproteins ranged from 24 to 72 hours ($\bar{X} \pm \text{SD}$, 32.4 ± 15.6 hours) for the five studies that reported this information.^{16, 19, 24-26} One study reported the multiple assessment of lipids and lipoproteins at each testing session.¹⁸

Training Program Characteristics

A description of the training program characteristics from the studies is shown in Table 2. Only five groups from four studies (45%) reported appropriate data on compliance to the

exercise protocol.^{18, 21, 24, 27} All exercise sessions were supervised. In relation to training modality, four studies were limited to cycle ergometry^{22, 25-27} while one each was limited to either walking and jogging²⁴ or aerobic dance types of activities.¹⁹ The remaining six studies used a combination of at least three or more of the following: walking, jogging, aerobic dance, cycle ergometry, games, and other miscellaneous activities.^{16-18, 20, 21, 23}

Outcomes

Overall results for primary and secondary outcomes—Pooled changes in primary and secondary outcomes using a random-effects model are shown in Table 3. Across all designs and categories, a small, nonsignificant exercise-minus control group reduction of 0.61% was observed for non-HDL-C. A statistically significant and large amount of between-study heterogeneity was found for non-HDL-C. However, no statistically significant publication bias was observed ($p = 0.32$).

Similar to non-HDL-C, no statistically significant exercise minus control group changes were found for TC, HDL-C, and body weight. A statistically significant and large amount of heterogeneity was found for HDL-C while a statistically significant and moderate amount of heterogeneity was found for changes in TC and body weight. No statistically significant publication bias was found for TC ($p = 0.08$) or HDL-C ($p = 0.22$). However, statistically significant publication bias was found for body weight ($p = 0.01$).

In contrast to non-HDL-C, TC, HDL-C and body weight, a statistically significant exercise minus control group decrease in percent body fat as well as a statistically significant exercise minus control group increase in VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$ was found. These improvements were equivalent to an approximate 7% decrease in percent body fat and an 8% increase in VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$. No statistically significant heterogeneity was observed for either percent body fat or VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$. In addition, no statistically significant publication bias was observed for changes in percent body fat ($p = 0.34$) or VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$ ($p = 0.40$).

Sensitivity analyses for non-HDL-C—With each study deleted from the model once, no statistically significant differences in non-HDL-C were found. In addition, cumulative meta-analysis, ranked by year, revealed that our non-HDL-C results have remained statistically nonsignificant since 1983. Furthermore, no statistically significant differences were found for any of our other sensitivity analyses, including meta-regression (99% CIs crossed zero for all).

DISCUSSION

The primary purpose of this study was to use the meta-analytic approach to examine the effects of aerobic exercise on non-HDL-C in children and adolescents. This is novel because it is the first time that any study has examined the effects of aerobic exercise on non-HDL-C in children and adolescents. Collectively, our results suggest that aerobic exercise has little effect on non-HDL-C in children and adolescents. This is in contrast to our previous meta-analytic work in which we found a statistically significant decrease of approximately 4% as a result of walking in adults.³¹ One of the possible reasons for this lack of improvement may have to do with the fact that the majority of subjects enrolled in the studies had normal baseline values of TC and HDL-C, the two variables from which non-HDL-C is calculated. Given these findings, it would appear plausible to suggest that future randomized controlled trials focus their research on children and adolescents with elevated levels of TC and low levels of HDL-C.

Despite extensive sensitivity analyses, we were unable to identify any statistically significant sources of heterogeneity for our non-HDL-C outcomes. One of the possible reasons for this may be the lack of reported data for variables that may contribute to this observed heterogeneity. Another possible reason may be the stringent criteria (99% confidence intervals) that we used for determining statistical significance. For example, while we found that greater reductions in non-HDL-C were associated with older age ($R = -0.54$), the 99% CI crossed zero (-0.26 to 0.89). Likewise, we also found that greater reductions in non-HDL-C were associated with higher training intensities ($R = -0.63$) but the 99% confidence interval also crossed zero (-0.24 to 0.93). However, since we were concerned about a Type I error given the large number of simple regression tests conducted as well as the fact that we were more interested in the precision of the correlation versus simply rejecting the null hypothesis, we chose to use 99% confidence intervals that did not cross zero for determining significance. Nevertheless, it would seem appropriate to suggest that future exercise training studies examine the association between changes in non-HDL-C and differences in age and training intensity since they accounted for 29% and 40% of the variability in non-HDL-C.

While secondary outcomes in this study, the 7% decrease in percent body fat and the 8% increase in VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$ suggest that aerobic exercise is important for improving these outcomes in children and adolescents. This is especially relevant given the increasing prevalence of overweight and obesity among children and adolescents and the subsequent risks associated with such.^{32, 33} Given these findings, participation in aerobic exercise should almost always be recommended for this age group. Currently, the Centers for Disease Control and Prevention recommend that children and adolescents participate in at least 60 minutes of moderate intensity physical activity on most days of the week, preferably daily. These include activities such as brisk walking, bicycling, and swimming.³⁴

Meta-analysis, like any type of review, is limited by the number of studies and data available for those studies. For example, we were surprised that only two studies were limited to subjects that were overweight or obese.^{21, 22} and only one provided data limited to females.²⁷ In addition, there was a lack of data provided by a number of studies for several key variables. These included race/ethnicity, number of hours that exercise was avoided prior to lipid assessment, and compliance to the exercise protocol. Furthermore, we were unable to conduct any type of multiple regression analysis because of missing data for different variables from different studies, a common occurrence with meta-analytic research.³⁵

In conclusion, the results of our study suggest that aerobic exercise does not reduce non-HDL-C but does decrease percent body fat and increase aerobic capacity in children and adolescents. However, a need exists for randomized controlled exercise trials that focus on children and adolescents with elevated lipid and lipoprotein levels.

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TABLE 1

Initial characteristics of subjects.

Variable	Exercise			Control		
	N	$\bar{x} \pm SD$	Range	N	$\bar{x} \pm SD$	Range
Age (yrs)	12	11.6 $\pm$ 2.8	8-16	11	11.8 $\pm$ 2.5	9-16
Height (cm)	13	150.0 $\pm$ 12.2	128-169	12	151.8 $\pm$ 12.9	133-174
Body weight (kg)	13	48.5 $\pm$ 14.0	27-75	12	50.0 $\pm$ 13.0	31-74
Body fat (%)	6	28.7 $\pm$ 13.0	15-45	5	28.2 $\pm$ 14.7	16-45
VO _{2max} (ml·kg ⁻¹ ·min ⁻¹)	8	41.8 $\pm$ 13.2	22-59	7	40.1 $\pm$ 12.0	23-61
TC (mg/dl)	13	162.8 $\pm$ 16.5	133-198	12	166.4 $\pm$ 21.2	137-213
HDL-C (mg/dl)	13	48.3 $\pm$ 10.3	38-67	12	46.3 $\pm$ 8.2	33-65
Non-HDL-C (mg/dl)	13	114.5 $\pm$ 11.4	95-132	12	120.1 $\pm$ 15.5	103-148

Notes: N, number of groups reporting data; $\bar{x} \pm SD$, mean $\pm$ standard deviation; Range represents group range means; VO_{2max}, maximum oxygen consumption; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol.

TABLE 2

Training program characteristics.

Variable	N	$\bar{x} \pm SD$	Range
Length (weeks)	13	10.4 $\pm$ 3.3	5 – 16
Frequency (times/week)	13	3.7 $\pm$ 0.8	3 – 5
Intensity (% VO _{2max})	11	74.9 $\pm$ 11.9	44-90
Duration (minutes/session)	11	47.7 $\pm$ 31.7	20-135
Compliance (%)	5	91.6 $\pm$ 8.3	80-100
Minutes per week	9	201 $\pm$ 189	60-675

Notes: N, number of groups reporting data; $\bar{x} \pm SD$, mean $\pm$ standard deviation; Range represents group ranges; Compliance, percentage of exercise sessions attended; Minutes per week calculated as frequency $\times$ duration.

TABLE 3

Primary and secondary outcomes.

Variable	Outcomes				Heterogeneity	
	N	$\bar{x} \pm \text{SEM}$	95% CI	Q	p	$I^2(\%)$
Non-HDL-C (mg/dl)	13	-0.7 $\pm$ 2.4	-5.4 to 5.0	43.6	<0.001 [†]	72.5
TC (mg/dl)	13	-1.0 $\pm$ 2.0	-4.8 to 2.9	19.7	0.07 [†]	39.0
HDL-C (mg/dl)	13	-1.2 $\pm$ 1.7	-4.5 to 2.2	150.8	<0.001 [†]	92.0
Body weight (kg)	10	1.1 $\pm$ 1.5	-1.9 to 4.0	16.3	0.06 [†]	44.9
Body fat (%)	5	-2.1 $\pm$ 0.5	-3.0 to -1.2 [*]	1.2	0.88	0
VO _{2max} (ml·kg ⁻¹ ·min ⁻¹)	8	3.4 $\pm$ 1.0	1.4 to 5.3 [*]	2.6	0.92	0

Notes: Outcomes data based on random effects model while heterogeneity data based on fixed-effects model; N, number of outcomes; $\bar{x} \pm \text{SEM}$, mean $\pm$ standard error of the mean; CI, 95% confidence interval; Q, heterogeneity statistic; p, probability value for Q; I^2 (%), percentage of heterogeneity, calculated as (Q-df)/Q * 100; Non-HDL-C, non-high-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; VO_{2max}, maximum oxygen consumption

* significantly different from zero (0)

[†] p $\leq$ 0.10.