Effect of Aerobic Exercise Training on Serum Levels of High-Density Lipoprotein Cholesterol

A Meta-analysis

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Background: Aerobic exercise is believed to reduce the risk of cardiovascular disease partially through increasing serum levels of high-density lipoprotein cholesterol (HDL-C). However, this effect varies considerably among exercise intervention studies.

Methods: Electronic database searches of MEDLINE (1966-2005) for randomized controlled trials that examined the effect of exercise training on HDL-C level.

Results: Twenty-five articles were included. Mean net change in HDL-C level was statistically significant but modest (2.53 mg/dL [0.065 mmol/L]; \(P < 0.001\)). Minimal weekly exercise volume for increasing HDL-C level was estimated to be 900 kcal of energy expenditure per week or 120 minutes of exercise per week. Univariate regression analysis indicated that every 10-minute prolongation of exercise per session was associated with an approximately 1.4-mg/dL (0.036-mmol/L) increase in HDL-C level. In contrast, there was no significant association between exercise frequency or intensity. Multiple meta-regression analyses demonstrated that subjects with a body mass index (calculated as weight in kilograms divided by height in meters squared) less than 28 and total cholesterol level of 220 mg/dL [5.7 mmol/L] or more experienced an approximately 2.1-mg/dL (0.054-mmol/L) larger increase in HDL-C level than those with a body mass index of 28 or more and total cholesterol level less than 220 mg/dL (5.7 mmol/L).

Conclusions: Regular aerobic exercise modestly increases HDL-C level. There appears to exist a minimum exercise volume for a significant increase in HDL-C level. Exercise duration per session was the most important element of an exercise prescription. Exercise was more effective in subjects with initially high total cholesterol levels or low body mass index.

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of death worldwide. Low blood levels of high-density lipoprotein cholesterol (HDL-C) are an independent risk factor for CVD. Cross-sectional data provide strong evidence that people who are more physically active have higher HDL-C levels. Thus, the value of regular aerobic exercise in increasing serum HDL-C level and in reducing the risk of CVD has received widespread acceptance. In contrast, results of aerobic exercise studies vary considerably, depending on the exercise program (eg, duration, intensity, or frequency) and characteristics of subjects at baseline. However, few studies have examined which characteristics would affect the response of HDL-C level to exercise training.

The objectives of this meta-analysis are to (1) estimate the minimum amount of exercise required to increase HDL-C level, (2) determine the exercise characteristics most effective in increasing HDL-C level, and (3) investigate the characteristics of subjects who most benefit from exercise through increases in HDL-C level. Clarifying these issues would help in establishing exercise programs to achieve better lipid profiles in a clinical setting.

METHODS

LITERATURE SEARCH

We searched MEDLINE (from 1966 to 2005) for all investigations of the effect of exercise on serum HDL-C levels. The search was restricted to studies using randomized controlled trials and that were published in English. Search phrases were related to exercise, aerobic capacity, and HDL-C (available on request from the authors). Reference lists of previous articles about exercise and HDL-C...
were also examined to identify additional articles. Our prespecified inclusion criteria were as follows: (1) aerobic training in adults (mean age, >20 years), (2) HDL-C measurements at baseline and at the end of the intervention, (3) training period of at least 8 weeks, and (4) inclusion of an exercise group and a concurrent nonexercise control group. Aerobic exercise was defined as rhythmic and repeated movements of the same large-muscle groups (eg, walking, bicycling, and continuous swimming) for at least 15 minutes.9 Co-intervention studies, such as those including a diet intervention, were also excluded because the effect of exercise training itself would be obscured. We also excluded studies of subjects having specific medical problems in which treatments such as with diet or drugs would influence the effect of exercise (eg, history of cancer, hemodialysis treatment, and coronary heart disease).

Included studies provided information on exercise characteristics such as duration (defined as time spent on 1 session of exercise), frequency (number of exercise sessions per week), relative intensity (proportion of exercise intensity to maximal aerobic capacity), and absolute intensity (expressed in metabolic equivalents [METs]). One MET corresponds to oxygen consumption of 3.5 mL/kg per minute. Fourteen studies10-22 were excluded because exercise volume could not be estimated in terms of total weekly energy expenditure (EE) and weekly exercise length (ie, time spent on exercise training per week). Accordingly, we excluded 4 trials that had resistance training or interval training components because of the difficulty in estimating EE.22,24-26

**VALIDITY ASSESSMENT AND DATA ABSTRACTION**

The methodologic quality of each included trial was assessed by means of the instrument described by Jadad et al.27 Two of our investigators independently reviewed each published article and extracted relevant information. Discrepancies were resolved by discussion with a third author. We collected data on subjects, exercise programs, and intervention outcomes (ie, change in HDL-C level). Mean age (in years), sex (indicated by percentage of men), HDL-C level (in milligrams per deciliter), maximal aerobic capacity represented by maximal or peak oxygen uptake (V02max or V02peak) (in milliliters per kilogram per minute), body weight (in kilograms), body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), percentage of body fat, triglyceride levels (in milligrams per deciliter), and total cholesterol (TC) level (in milligrams per deciliter) were extracted as characteristics of subjects. The characteristics of the exercise intervention included exercise duration, frequency, relative intensity, and absolute intensity.

Relative intensity was extracted directly from studies or estimated from the exercise heart rate reserve or a proportion of exercise heart rate to maximum according to a previously established formula.26-28 Absolute intensity was calculated by multiplying relative intensity, ie, percentage of V02peak or V02max, by maximal aerobic capacity. In 3 studies,30-32 absolute intensity was estimated by linear regression analysis of walking speed (in miles per hour) with exercise intensity in METs according to Hendelman et al.33 Exercise volume was assessed by both total weekly exercise length and total weekly estimated EE. Weekly EE was calculated by multiplying exercise intensity (1 MET corresponds to 0.0175 kcal) by weekly exercise length and body mass.

Mean difference in HDL-C change after training between exercise and nonexercise control groups (MDHC) was calculated as the net HDL-C effect of exercise training. Standard error was directly extracted or otherwise calculated from standard deviation, confidence intervals, or P values for HDL-C effects within groups. To estimate standard error, a correlation of 0.5 between variances at baseline and at follow-up within each group was assumed according to Follmann et al34 as follows:

\[
\text{SE} = \sqrt{\frac{(\text{SE}_{\text{baseline}})^2 + (\text{SE}_{\text{follow-up}})^2}{2}} \times 0.5 \times (\text{SE}_{\text{baseline}} \times \text{SE}_{\text{baseline}})
\]

Each MDHC was weighted according to the inverse of its variance and the average. Weighted MDHCs were pooled with a random-effects model35 (ie, pooled MDHC). The \( \chi^2 \) values were calculated to assess for heterogeneity among studies.

We assessed publication bias primarily by means of a funnel plot, in which each MDHC was plotted against the reciprocal of standard error. Publication bias was secondarily assessed by 2 formal tests: the Begg-adjusted rank correlation test and Macaskill regression asymmetry test.16,37

To investigate the minimal volume of prescribed exercise above which the HDL-C level significantly started to rise, trials were stratified into 4 intervals by weekly estimated EE or weekly exercise length. Overall and each pooled MDHC after stratification were standardized; results were indicated by a z score. A weighted linear meta-regression analysis was performed to examine whether the change in HDL-C level was mediated by characteristics of exercise programs or of subjects. In all meta-regression analyses, each trial was weighted according to exercise group size. The correlation coefficient (r) was calculated to demonstrate the important predictors of an elevation in HDL-C level. To determine which of the subjects’ baseline characteristics and which exercise characteristics (ie, duration, frequency, and relative or absolute intensity) influenced an increase in HDL-C level, multivariate analysis was performed on the
Table 1. Population Characteristics in Randomized Controlled Trials of Exercise Intervention and HDL-C

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y</th>
<th>Sex, % M</th>
<th>Ex-n (Pre–Ex-n*)</th>
<th>C-n</th>
<th>HDL-C, mg/dL</th>
<th>TC, mg/dL</th>
<th>TG, mg/dL</th>
<th>BF, %</th>
<th>BMI</th>
<th>Max Cap†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldred et al,30 1995</td>
<td>49</td>
<td>0</td>
<td>11 (13)</td>
<td>13</td>
<td>61</td>
<td>207</td>
<td>77</td>
<td>ND</td>
<td>ND</td>
<td>39.7</td>
</tr>
<tr>
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<td>59</td>
<td>100</td>
<td>20 (23)</td>
<td>15</td>
<td>36</td>
<td>230</td>
<td>89</td>
<td>27.1</td>
<td>ND</td>
<td>30.6</td>
</tr>
<tr>
<td>Busby et al,44 1985</td>
<td>50</td>
<td>0</td>
<td>12</td>
<td>12</td>
<td>50</td>
<td>173</td>
<td>71</td>
<td>ND</td>
<td>22.6</td>
<td>23.6</td>
</tr>
<tr>
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<td>63</td>
<td>100</td>
<td>100 (113)</td>
<td>100</td>
<td>45</td>
<td>229</td>
<td>55</td>
<td>ND</td>
<td>26.2</td>
<td>30.0</td>
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<tr>
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<td>20-40</td>
<td>0</td>
<td>16 (25)</td>
<td>10</td>
<td>54</td>
<td>180</td>
<td>78</td>
<td>29.3</td>
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<td>75</td>
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<td>15</td>
<td>15</td>
<td>44</td>
<td>182</td>
<td>128</td>
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<td>20</td>
<td>17</td>
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<td>203</td>
<td>133</td>
<td>28.1</td>
<td>ND</td>
<td>28.5</td>
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<tr>
<td>Houmard et al,50 1994</td>
<td>48</td>
<td>100</td>
<td>12</td>
<td>7</td>
<td>35</td>
<td>200</td>
<td>155</td>
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<td>43</td>
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<td>44 (50)</td>
<td>46</td>
<td>48</td>
<td>263</td>
<td>131</td>
<td>ND</td>
<td>43.5</td>
<td>†</td>
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<td>49</td>
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<td>29 (30)</td>
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<td>143</td>
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<td>15 (17)</td>
<td>19</td>
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<td>130</td>
<td>ND</td>
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<td>17</td>
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<td>205</td>
<td>103</td>
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<td>Niemelä et al,57 2002</td>
<td>50</td>
<td>0</td>
<td>25</td>
<td>20</td>
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<td>217</td>
<td>82</td>
<td>ND</td>
<td>ND</td>
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<td>Ready et al,58 1995</td>
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<td>15 (19)</td>
<td>10</td>
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<td>157</td>
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<td>16</td>
<td>11</td>
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<td>Sunami et al,62 1999</td>
<td>56</td>
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<td>Thomas et al,63 1984</td>
<td>18-32</td>
<td>100</td>
<td>5</td>
<td>6</td>
<td>39</td>
<td>175</td>
<td>82</td>
<td>13.8</td>
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<td>56.0</td>
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<tr>
<td>Thomas et al,64 1985</td>
<td>100</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>40</td>
<td>171</td>
<td>83</td>
<td>12.8</td>
<td>ND</td>
<td>54.5</td>
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<tr>
<td>Wood et al,65 1983</td>
<td>23</td>
<td>100</td>
<td>11</td>
<td>8</td>
<td>49</td>
<td>161</td>
<td>110</td>
<td>ND</td>
<td>ND</td>
<td>50.0</td>
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<tr>
<td>Wood et al,66 1983</td>
<td>46</td>
<td>100</td>
<td>46 (48)</td>
<td>33</td>
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<td>Wooi-May et al,67 1998</td>
<td>57</td>
<td>100</td>
<td>10</td>
<td>10</td>
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<td>114</td>
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<tr>
<td>Wooi-May et al,68 1999</td>
<td>55</td>
<td>100</td>
<td>5</td>
<td>4</td>
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<td>224</td>
<td>121</td>
<td>ND</td>
<td>26.3</td>
<td>34.3</td>
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</tbody>
</table>

Abbreviations: BF, body fat; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); C-n, number in control group; Ex-n, number in exercise group; HDL-C, high-density lipoprotein cholesterol; Max Cap, maximal aerobic capacity, assessed by maximal or peak oxygen uptake; ND, no data; TC, total cholesterol; TG, triglycerides.

SI conversion factors: To convert HDL-C and TC to millimoles per liter, multiply by 0.0259; TG to millimoles per liter, multiply by 0.0113.

*Number in exercise group at preintervention.
†Estimated by energy expenditure and oxygen consumption during exercise; expressed as milliliters of oxygen per kilogram per minute.

RESULTS

STUDY CHARACTERISTICS

There were 137 potentially relevant articles on randomized controlled trials based on the search terms (Figure 1). Of 32 studies meeting the initial inclusion criteria, 4 articles were excluded because the pattern of change in energy intake differed between exercise and control groups, and 2 were excluded because of a crossover design in which carryover effects could not be ignored.

Finally, 25 articles (33 trials) met our inclusion criteria. Sample sizes varied between 9 and 200, with a total of 1404 subjects (mean age range, 23-75 years) (Table 1). The mean intervention period was 27.4 weeks. Subjects were not limited to specific ethnic groups, but in many studies information on ethnicity was lacking.

The quality of trials was assessed according to the scale described by Jadad et al,27 with each trial evaluated according to randomization, double-blinding, withdrawals, and dropouts. The mean (SD) score was comparatively low (1.5 [0.5] of a possible 5 points). The quality assessment criterion that permitted discrimination between studies involved withdrawals and dropouts. Twelve trials reported the number of withdrawals and reasons for withdrawal, while 13 trials did not. The dropout rate of subjects ranged from 4% to 65%.
to 39%. In none of the 25 randomized controlled trials were methods of randomization described. Mean prescribed exercise interventions included a mean of 3.7 sessions per week, each averaging 40.5 minutes (Table 2). Mean estimated relative and absolute intensity of the aerobic exercise were 64.8% of maximal aerobic capacity and 5.3 METs, respectively. Mean estimated weekly EE was 1019 kcal/wk.

**Table 2. Exercise Intervention Characteristics in Randomized Controlled Trials of Exercise Intervention and HDL-C**

<table>
<thead>
<tr>
<th>Source</th>
<th>Weeks</th>
<th>Freq</th>
<th>Prescribed Exercise Intensity</th>
<th>D, min</th>
<th>Weekly EE, kcal</th>
<th>MET</th>
<th>Type of Exercise</th>
<th>Dietary Instruction*</th>
<th>Dietary Record†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldred et al30</td>
<td>12</td>
<td>6.1</td>
<td>Brisk walking; mean exercise intensity, 74% of HRmax</td>
<td>25</td>
<td>877</td>
<td>5.2</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Baker et al45</td>
<td>20</td>
<td>3.0</td>
<td>65%-75% of HRR</td>
<td>48</td>
<td>1208</td>
<td>5.9</td>
<td>W/J</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Busby et al46</td>
<td>12</td>
<td>3.0</td>
<td>70%-80% of HRmax</td>
<td>30</td>
<td>299</td>
<td>3.0</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Cunningham et al47</td>
<td>52</td>
<td>2.5</td>
<td>(&gt;0.60 maximal METs/10)% of HRR</td>
<td>32</td>
<td>578</td>
<td>5.9</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Duncan et al48</td>
<td>24</td>
<td>5.0</td>
<td>Walking speed, 8.3 km/h</td>
<td>36</td>
<td>1294</td>
<td>6.7</td>
<td>W/J</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Fahlman et al49</td>
<td>12</td>
<td>3.0</td>
<td>70% of HRR</td>
<td>45</td>
<td>1293</td>
<td>5.1</td>
<td>W/J</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Grandjean et al50</td>
<td>12</td>
<td>4.0</td>
<td>Progressively increased intensity (from 60%-70% of VO2max to 70%-80% of VO2max)</td>
<td>40</td>
<td>1200</td>
<td>4.9</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hournard et al50</td>
<td>14</td>
<td>3.8</td>
<td>Progressively increased intensity (from 70%-80% of HRmax to 85%-95% of HRmax and exercise duration (30 min/session to 45 min/session)</td>
<td>41‡</td>
<td>1245</td>
<td>4.9</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Huttunen et al51</td>
<td>16</td>
<td>3.0</td>
<td>Progressively increased intensity (from 40% of HRR to 66% of HRR) 15 min warming up; 10 min cooling down</td>
<td>38§</td>
<td>927</td>
<td>6.0</td>
<td>O</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Juneau et al52</td>
<td>24</td>
<td>5.0</td>
<td>Mean exercise intensity, 72% of HRmax</td>
<td>47</td>
<td>1725</td>
<td>5.3</td>
<td>W/J</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Kokkinos et al63</td>
<td>16</td>
<td>3.0</td>
<td>Mean exercise intensity, 69% of HRmax</td>
<td>54</td>
<td>1175</td>
<td>3.9</td>
<td>W/J</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Kraus et al64</td>
<td>26</td>
<td>3.4</td>
<td>40%-55% of VO2peak</td>
<td>52</td>
<td>920</td>
<td>3.3</td>
<td>O</td>
<td>Y</td>
<td>Y</td>
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<td>Linde et al65</td>
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<td>70% of HRmax</td>
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<td>O</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Nieman et al67</td>
<td>12</td>
<td>5.0</td>
<td>Progressively increased intensity (from 65%-70% of HRmax to 70%-80% of HRmax)</td>
<td>45</td>
<td>1151</td>
<td>3.3</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Ready et al68</td>
<td>26</td>
<td>4.9</td>
<td>54% of HRR</td>
<td>54</td>
<td>1156</td>
<td>3.3</td>
<td>W/J</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Santiago et al69</td>
<td>40</td>
<td>4.0</td>
<td>Treadmill walking, 4.8 km/session; mean exercise intensity, 72% of HRmax</td>
<td>50</td>
<td>875</td>
<td>3.9</td>
<td>W/J</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Sjöko et al70</td>
<td>12</td>
<td>5.0</td>
<td>6 METs</td>
<td>67</td>
<td>3088</td>
<td>5.3</td>
<td>W/J</td>
<td>Y</td>
<td>Y</td>
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<td>Stensel et al71</td>
<td>52</td>
<td>2-3</td>
<td>Walking speed, 1.90 m/s</td>
<td>28</td>
<td>536</td>
<td>5.5</td>
<td>W/J</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Sunami et al72</td>
<td>26</td>
<td>2.4</td>
<td>2-4 sessions/wk</td>
<td>60</td>
<td>570</td>
<td>3.4</td>
<td>C</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Thomas et al73</td>
<td>12</td>
<td>3.0</td>
<td>75% of HRmax</td>
<td>42§</td>
<td>1330</td>
<td>7.8</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Thomas et al74</td>
<td>12</td>
<td>3.0</td>
<td>75% of HRmax</td>
<td>24§</td>
<td>664</td>
<td>7.7</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Wood et al75</td>
<td>52</td>
<td>3-5</td>
<td>70%-85% of maximal aerobic capacity</td>
<td>28§</td>
<td>1117</td>
<td>7.6</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Woolf-May et al76</td>
<td>18</td>
<td>6.0</td>
<td>68% of VO2max</td>
<td>23</td>
<td>828</td>
<td>4.2</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Woolf-May et al77</td>
<td>18</td>
<td>6.0</td>
<td>68% of VO2max</td>
<td>23</td>
<td>623</td>
<td>4.0</td>
<td>W/J</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Abbreviations: C, cycling or bicycle ergometer; D, exercise duration per session; Freq, exercise frequency expressed as number of exercise sessions per week; HDL-C, high-density lipoprotein cholesterol; HRmax, maximal heart rate; HRR, heart rate reserve; MET, absolute exercise intensity in metabolic equivalents (1 MET corresponds to 3.5 mL of O2/kg per minute); N, no (ie, information was not provided); O, other type of aerobic training programs (eg, swimming, skiing, or use of an elliptical trainer); W/J, walking or jogging; weekly EE, estimated energy expenditure per week; VO2max, maximal oxygen uptake; VO2peak, peak oxygen uptake; Y, yes (ie, information was provided).

*Subjects were instructed to maintain regular eating habits or not to attempt to change body mass.
†Dietary intake was recorded before and after the intervention in the exercise and nonexercise groups.
‡Mean exercise duration per session during intervention.}
§Estimated by energy expenditure and oxygen consumption during exercise.
[HRR corresponds to 0.5 minute of exercise training.]

**EFFECT OF EXERCISE ON HDL-C LEVELS**

Each MDHC and the pooled MDHC are shown in Figure 2. Overall net change in HDL-C level was modest.
although statistically significant (2.53 mg/dL [0.065 mmol/L]; 95% confidence interval, 1.36–3.70 mg/dL [0.035–0.096 mmol/L]).

**EVALUATION OF PUBLICATION BIAS**

**Figure 3** shows a funnel plot for the visual assessment of publication bias. Both the Begg adjusted rank test and the Macaskil regression asymmetry test indicated no evidence of potential publication bias (P=.67 for Begg test; P=.97 for Macaskil test). One study (black square in Figure 3) was statistically an outlier (t = 4.29), and the following meta-analyses were performed after exclusion of this study.

**RELATIONSHIP BETWEEN EXERCISE VOLUME AND HDL-C LEVEL**

Findings from stratified meta-analyses based on weekly EE and weekly exercise length are presented in **Table 3**. For 21 trials in which the weekly estimated EE was greater than 900 kcal, the pooled MDHC was significant (z score, 5.16; P<.001), but it was not significant for 13 trials in which EE did not exceed 900 kcal/wk (z score, 0.95; P=.34). For 25 trials in which the weekly total exercise length was more than 120 minutes, pooled MDHC was significant (z score, 3.60; P<.001); no significance was observed for 9 trials in which weekly exercise length was not more than 120 minutes (z score, 1.15; P=.25).

**EFFECT OF EXERCISE CHARACTERISTICS ON CHANGE IN HDL-C LEVEL AFTER EXERCISE TRAINING**

We calculated the correlation regression to explore which characteristic of an exercise program (ie, duration, frequency, and absolute intensity) was the best predictor of an increase in HDL-C level (Figure 4). Univariate analysis showed that exercise duration was the strongest predictor of MDHC, and each 10-minute increase in exercise duration corresponded to an approximately 1.4-mg/dL (0.036 mmol/L) net increase in HDL-C level when the duration ranged from 23 to 74 minutes per session. Furthermore, we investigated the effect of a relatively short session of continuous exercise because about 30 minutes of exercise per day has been recommended for maintaining good health. However, the pooled MDHC was not significant when exercise duration was 30 minutes or less per session (0.27 mg/dL [0.007 mmol/L]; 95% confidence interval, -2.04 to 2.59 mg/dL [−0.053 to 0.067 mmol/L]). The MDHC was not associated with other exercise measures such as frequency, absolute intensity, or relative intensity.

Since exercise volume is often quite limited in daily life, multivariate analyses of exercise characteristics and MDHC were performed by adjusting for weekly EE or weekly exercise length (**Table 4**). When weekly EE was controlled for, exercise duration remained positively associated with MDHC, while exercise intensity did not influence

**Study**  | **MDHC (95% CI), mg/dL**
---|---
Fahlin et al  | 9.0 (0.9 to 17.1)
Baker et al  | 8.0 (1.1 to 14.9)
Juneau et al  | 7.2 (1.0 to 13.4)
Grandjean et al  | 6.1 (1.6 to 10.6)
Sunami et al  | 6.0 (1.2 to 10.8)
Thomas et al  | 5.9 (1.2 to 10.6)
Kraus et al  | 4.9 (1.2 to 8.7)
Huttunen et al  | 4.6 (1.2 to 7.9)
Sopko et al  | 3.8 (0.1 to 7.6)
Woolf-May et al  | 3.5 (−6.3 to 12.3)
Sanjogo et al  | 3.4 (−6.9 to 13.7)
Thomas et al  | 3.0 (−6.7 to 12.6)
Ready et al  | 2.7 (−6.9 to 12.3)
Duncan et al  | 2.3 (−8.9 to 13.5)
Duncan et al  | 2.3 (−8.8 to 13.4)
Kokkinos et al  | 2.0 (−7.3 to 11.3)
Cunningham et al  | 1.5 (−3.4 to 6.4)
Duncan et al  | 1.5 (−9.5 to 12.6)
Wood et al  | 1.3 (−2.7 to 5.3)
Kraus et al  | 1.3 (−6.1 to 8.7)
Woolf-May et al  | 1.2 (−14.7 to 15.1)
Juneau et al  | 1.0 (−6.1 to 8.1)
Kraus et al  | 0.9 (−7.7 to 9.5)
Kokkonen-Harjula et al  | 0.8 (−1.9 to 3.6)
Alfred et al  | 0.4 (−9.0 to 9.8)
Busby et al  | 0.0 (−6.0 to 6.0)
Stensel et al  | 0.0 (−11.8 to 11.8)
Nieman et al  | 0.4 (7.2 to 6.5)
Thomas et al  | 1.0 (−8.7 to 6.7)
Thomas et al  | 1.0 (−9.2 to 7.2)
Hournard et al  | 1.1 (−7.9 to 5.7)
Lindheim et al  | 2.2 (−11.2 to 6.8)
Woolf-May et al  | 3.5 (−17.7 to 10.7)
Woolf-May et al  | 3.5 (−20.8 to 13.8)
**Total**  | 2.53 (1.36 to 3.70)

![Figure 2](http://archinte.jamanetwork.com/pdfaccess.ashx?url=data/journals/intemed/5593/)
MDHC. When we controlled for weekly exercise length, exercise duration was positively and exercise frequency was negatively associated with MDHC. Univariate and multivariate analyses indicated that exercise duration was the most important predictor of MDHC.

EFFECTS OF SUBJECT CHARACTERISTICS ON CHANGE IN HDL-C LEVEL BY EXERCISE TRAINING

Multivariate analysis was performed by means of regression models to investigate the extent to which characteristics of subjects independently contributed to the change in HDL-C level (Table 5). Two stepwise regression analyses using model 1 and model 2 showed that subjects with a higher TC level or who were less obese responded better to exercise training. In model 2, in subjects with a mean TC level of 220 mg/dL (5.7 mmol/L) or greater and mean BMI less than 28, exercise training resulted in an average of 2.1-mg/dL (0.054 mmol/L) (5.1 times) larger net elevation in HDL-C level than when the mean TC level was less than 220 mg/dL (5.7 mmol/L) and mean BMI was 28 or greater. By contrast, age, percentage of men, HDL-C level, and aerobic capacity were not significant predictors of MDHC.

COMMENT

Our meta-analysis indicated that the effect of aerobic training resulted in a 2.53-mg/dL (0.065 mmol/L) elevation of net HDL-C change (Figure 2). In a previous observational study,60 every 1-mg/dL (0.026 mmol/L) increment in HDL-C level was reported to be associated with a 2% and 3% decreased risk of CVD in men and women, respectively. If this observation were applied to our results, the increase in HDL-C level by exercise determined by this analysis would be, by a rough estimate, result in a CVD risk reduced by approximately 5.1% in men and 7.6% in women. This is potentially of substantial importance in public health, although the effect of reducing cardiovascular risk by increasing HDL-C level might be smaller than that by use of medications such as fibrates or niacin.60 However, the modest elevation in HDL-C level demonstrated by this analysis is of clinical importance and was not far from findings of previous meta-analyses wherein Kelley et al70 and Halbert et al71 reported mean net elevations in HDL-C level of 1.2 mg/dL (0.031 mmol/L) and 1.9 mg/dL (0.05 mmol/L), respectively.

The current results support those in the review by Durstine et al72 that a minimum exercise volume may exist above which an HDL-C elevation occurs. However, the required exercise volume to produce a significant change in HDL-C differed between our findings and theirs. They also reported that weekly EE greater than 1200 kcal/wk was frequently associated with elevations in HDL-C level, while our analysis
dicated a value of approximately 900 kcal of weekly EE (Table 3). The reasons for this large discrepancy might be that their review included nonrandomized controlled trial studies or studies lacking nonexercise control groups, and might therefore have lower internal validity.

Before this analysis, it was inconclusive whether exercise characteristics (eg, duration, frequency, or intensity) affect a change in HDL-C level. Differences in controlled variables among studies, such as exercise duration and volume, could account for the varied results. Therefore, we performed both unadjusted (Figure 4) and multivariate (Table 4) analyses (adjusted for estimated weekly exercise volume) to investigate the association between each exercise characteristic and the change in HDL-C level. Exercise intensity was not associated with MDHC when adjusted for weekly EE. This result indicated that vigorous exercise intensity was not necessary if EE by exercise is sufficient, which supported previous results.

Controlling for weekly exercise length and exercise duration (not exercise frequency) was positively associated with MDHC (Table 4). This suggests that in improving blood HDL-C values, increasing time per session is better than performing multiple brief exercise sessions when total time for exercise is limited, as is the case for many people. Although the Centers for Disease Control and Prevention and the American College of Sports Medicine recommend about 30 minutes of moderate-intensity physical activity such as brisk walking on most (or preferably all) days, our analyses suggest that a longer duration per session of continuous exercise than that recommended is necessary for a significant increase in HDL-C level. However, no study in this analysis reported weekly exercise frequency of twice or less; the frequency in those studies ranged from 2.3 to 6.1 workouts per week. Therefore, additional research is needed to determine the minimal exercise frequency required to modify HDL-C levels.

It is important from a clinical viewpoint to examine whether exercise training is more effective in improving HDL-C level in subjects with low HDL-C levels than in those with values in the normal range. However, few studies have investigated the effect of the initial HDL-C level on the elevation in HDL-C level.

### Table 4. Relationships Between Exercise Characteristics and Mean Difference in HDL-C Change Between Exercise and Control Groups

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Coefficient (SE)</th>
<th>r</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D*</td>
<td>0.15 (0.04)</td>
<td>0.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Freq</td>
<td>−0.56 (0.55)</td>
<td>−0.18</td>
<td>.31</td>
</tr>
<tr>
<td>% Max cap</td>
<td>−0.02 (0.05)</td>
<td>−0.11</td>
<td>.76</td>
</tr>
<tr>
<td>MET</td>
<td>−0.22 (0.34)</td>
<td>−0.12</td>
<td>.52</td>
</tr>
<tr>
<td>Model 2†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D*</td>
<td>0.21 (0.06)</td>
<td>0.54</td>
<td>.001</td>
</tr>
<tr>
<td>Freq</td>
<td>−1.79 (0.59)</td>
<td>−0.48</td>
<td>.005</td>
</tr>
<tr>
<td>% Max cap</td>
<td>0.02 (0.05)</td>
<td>0.03</td>
<td>.63</td>
</tr>
<tr>
<td>MET</td>
<td>0.16 (0.32)</td>
<td>0.08</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviations: D, exercise duration per week; Freq, exercise frequency; HDL-C, high-density lipoprotein cholesterol; % Max cap, percentage of exercise intensity to maximal aerobic capacity; MET, absolute exercise intensity in metabolic equivalents.

*Adjusted for weekly exercise energy expenditure.
†Adjusted for weekly exercise length.
after long-term exercise training. 22,59,75 Moreover, the increase in HDL-C level in those with low HDL-C levels could be explained as a phenomenon of regression to the mean. Additional studies are necessary to clarify the relationship between baseline HDL-C level and response to exercise training. In contrast, this analysis suggests that TC value is more important than HDL-C level in distinguishing exercise responders (Table 5), although the biological mechanism is still unknown.

Our multiple regression analyses demonstrated that it is difficult for obese subjects to increase HDL-C levels by exercise training, which supports the result of Nicklas et al.,76 showing that HDL-C changes after training correlated negatively with the initial BMI. Moreover, it has been reported that improvement in lipid metabolism was related to exercise-induced weight and body fat loss.77,80 We speculate that improvement in HDL-C levels in obese subjects is difficult through exercise alone and that reducing body weight is more effective through combining caloric restrictions with exercise.

The present study has several limitations and evokes suggestions for future studies. The first limitation is that our meta-analyses are confined to published studies. Although we did not find evidence of publication bias either graphically or statistically by using the Begg or Ma-caskil method,36,37 these tests do not necessarily have statistically sufficient power to detect the publication bias. Therefore, while we are fairly confident that positive publication bias does not exist, we cannot rule it out entirely. In addition, double-masked methods are essentially impossible in exercise intervention studies. Second, most trials did not provide data on the period from the last exercise session to the measurement, so the exercise possibly raised HDL-C level as an acute effect. Third, in most included trials, data on alcohol intake, which could influence HDL-C levels, were not considered. In fact, we excluded studies investigating a combined effect of exercise and change in alcohol intake.81,82 Further studies of the following topics are suggested: (1) comparison of expected reduction of cardiovascular risk between by elevation of HDL-C level and improvement of aerobic fitness,83 (2) ethnic or sex differences in increases in HDL-C level through exercise, and (3) review of the effectiveness of resistance training on improving HDL-C level.84,85

Our study has several strengths. We used very strict inclusion criteria, enabling extraction of genuine effects of aerobic exercise with minimal effects from confounding factors. For example, we included only studies without significant changes in dietary intake. Therefore, we could more accurately assess the relationship between exercise itself and increases in HDL-C level than previous meta-analyses76,77 that included trials with resistance training components or trials with dietary modifications including change in energy intake during the intervention. In addition, we clarified exercise characteristics most suitable for improving HDL-C levels by different types of analysis, eg, univariate (unadjusted) and multivariate (adjusting for weekly EE or weekly exercise length) analyses. This approach is essential and practical because most individuals have limitations on volume of or time for exercise.

In conclusion, the average net increase in HDL-C level by exercise itself was modest but highly significant. The minimal exercise volume at which a statistically significant elevation in HDL-C level occurred was estimated to be approximately 90 kcal of weekly EE or 120 minutes of weekly total exercise length. Each 10-minute increase in exercise duration corresponded to an approximately 1.4-mg/dL (0.036-mmol/L) net increase in HDL-C level. Exercise was suggested to be more effective in less obese subjects (BMI < 28) and in those with a higher TC level (≥ 220 mg/dL [≥ 5.7 mmol/L]). The mechanism for this effect should be investigated in the future.

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Author Contributions: Dr H. Sone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kodama, Saito, Nomizu, Suzuki, Kondo, Yamada, H. Sone. Acquisition of data: Kodama, Tanaka, Saito, Shu, Yamamoto, Ohashi, and H. Sone. Analysis and interpretation of data: Kodama, Tanaka, Saito, Y. Sone, Shimano, Kondo, Ohashi, Yamada, and H. Sone. Drafting of the manuscript: Kodama, Saito, and H. Sone. Critical revision of the manuscript for important intellectual content: Kodama, Tanaka,

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**Table 5. Significant Predictors Among Characteristics of Subjects for Mean Difference in HDL-C Change Between Exercise and Control Groups**

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter*</th>
<th>Coefficient (SE)</th>
<th>Cumulative r²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1†</td>
<td>TC</td>
<td>0.04 (0.02)</td>
<td>0.14</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>Men vs women‡</td>
<td>−2.44 (1.12)</td>
<td>0.18</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>% BF</td>
<td>−0.14 (0.07)</td>
<td>0.28</td>
<td>.05</td>
</tr>
<tr>
<td>Model 2§</td>
<td>TC</td>
<td>0.05 (0.02)</td>
<td>0.14</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.35 (0.15)</td>
<td>0.26</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: BF, body fat; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

*Mean age (years), sex (percentage of men), HDL-C level (milligrams per deciliter), maximal aerobic capacity (milliliters per kilogram per minute), body mass index, percentage of body fat, triglyceride level (milligrams per deciliter), and total cholesterol level (milligrams per deciliter) were entered as the independent variables. All entered variables were adjusted for relative intensity, exercise duration, exercise frequency, and intervention period.

†In model 1, BMI was excluded from the independent variables because of multicolinearity.

‡Mean differences in increase in HDL-C level for men vs women, milligrams per deciliter.

§In model 2, percentage of BF was excluded from the independent variables because of multicolinearity with percentage of BF.

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REFERENCES


