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1 **Association of Resistance Exercise with the Incidence of Hypercholesterolemia in Men**

2

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6

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8

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22

1 **Abstract**

2 **OBJECTIVES** To examine the associations of resistance exercise, independent of and  
3 combined with aerobic exercise, with the risk of developing hypercholesterolemia in men.

4 **PATIENTS AND METHODS** A total of 7,317 men, aged 18-83 years (mean 46), without  
5 hypercholesterolemia at baseline were included. Participants received extensive preventive  
6 medical examinations at the Cooper Clinic in Dallas, Texas between January 1, 1987, and  
7 December 31, 2006. Frequency (times/week) and total amount (minutes/week) of resistance  
8 and aerobic exercise were determined by self-report. Hypercholesterolemia was defined as  
9 total cholesterol  $\geq$ 240 mg/dL or physician-diagnosis.

10 **RESULTS** During median follow-up of 4 years (minimum, 0.1 year; maximum, 19 years),  
11 1,430 men (20%) developed hypercholesterolemia. Individuals meeting the resistance  
12 exercise guidelines ( $\geq$ 2 days/week) had a 13% lower risk of developing hypercholesterolemia  
13 (HR, 0.87; 95% CI, 0.76- 0.99;  $P=.04$ ) after adjustment for general characteristics, lifestyle  
14 factors and aerobic exercise. In addition, less than 1 hour/week and 2 sessions/week of  
15 resistance exercise were associated with 32% and 31% lower risks of hypercholesterolemia  
16 (HR, 0.68; 95% CI, 0.54-0.86;  $P=.001$  and HR, 0.69; 95% CI, 0.54-0.88;  $P=.003$ ),  
17 respectively, compared to no resistance exercise. Higher levels of resistance exercise did not  
18 show benefits. Meeting both resistance and aerobic exercise ( $\geq$ 500 MET-minutes/week)  
19 guidelines lowered the risk of developing hypercholesterolemia by 22% (HR, 0.78; 95% CI,  
20 0.68-0.91;  $P=.002$ ), compared to meeting none of the guidelines.

21 **CONCLUSIONS** Compared to no resistance exercise, less than 1 hour/week of resistance  
22 exercise, independent of aerobic exercise, is associated with a significantly lower risk of  
23 developing hypercholesterolemia in men. However, the lowest risk of hypercholesterolemia  
24 was found at 58 minutes per week of resistance exercise. This suggests that resistance  
25 exercise should be encouraged to prevent hypercholesterolemia in men. However, future

1 studies with a more rigorous analysis including significant potential confounders (e.g., diet,  
2 medications) are warranted.

3

4 **KEYWORDS** Resistance exercise; hypercholesterolemia; physical activity; cardiovascular  
5 risk factor; cholesterol

6

#### 7 **Abbreviations**

8 AIC = akaike Information Criterion

9 BMI = body mass index

10 CI = confidence interval

11 CVD = cardiovascular disease

12 HR = hazard ratio

13 PA = physical activity

## 1 **Introduction**

2 Cardiovascular disease (CVD) is the leading cause of death in the United States and many  
3 other countries, especially throughout the Westernized World. <sup>1</sup> Hypercholesterolemia, one of  
4 the most important risk factors for CVD <sup>2,3</sup>, occurs in 13.1% of US adult population. <sup>4</sup>  
5 Regular physical activity (PA) is recommended for treating and preventing  
6 hypercholesterolemia. <sup>5</sup> Aerobic exercise uses large muscle groups continuously and  
7 rhythmically, and its benefits on serum cholesterol levels are well-documented. <sup>6-8</sup> On the  
8 other hand, resistance exercise is based on repeated bouts of isolated muscle groups and may  
9 therefore result in different physiological effects or health benefits. <sup>9</sup> Evidence for the  
10 different molecular pathways to reduce total cholesterol by aerobic or resistance exercise is  
11 scarce. However, earlier studies showed the different effects of aerobic and resistance  
12 exercise on cardiovascular health outcomes. <sup>9-11</sup> Meta-analyses of resistance exercise training  
13 on total cholesterol levels found contradictory results. <sup>12-14</sup> However, these trials had relatively  
14 short intervention periods and a lack of statistical power. <sup>11</sup> A cross-sectional study showed  
15 that engagement in regular resistance exercise was associated with lower total cholesterol  
16 levels. <sup>15</sup> However, evidence regarding the effects of resistance exercise on the development  
17 of hypercholesterolemia from large prospective cohort studies is very limited. The aim of this  
18 study is to examine the association of resistance exercise, independent of and combined with  
19 aerobic exercise, with the risk of developing hypercholesterolemia in relatively healthy men.  
20 We hypothesize that resistance exercise lowers the risk of developing hypercholesterolemia,  
21 and participating in both resistance and aerobic exercise is superior in decreasing the risk of  
22 hypercholesterolemia, when compared with each individual type of exercise alone.

23

## 24 **Methods**

25 *Study Population*

1 Men were included if they had baseline measurements of self-reported resistance exercise and  
2 other covariates, performed comprehensive medical examinations at baseline, and participated  
3 in at least one follow-up clinical examination. Among 11,601 men meeting the above  
4 inclusion criteria, 848 were excluded due to a history of myocardial infarction, stroke, or  
5 cancer at baseline. In addition, 3,436 men were excluded as a result of hypercholesterolemia  
6 at baseline. The final sample included 7,317 men aged 18-83 years at baseline (mean age 46  
7 years, SD 10). Women were excluded from the study because of a relatively small proportion  
8 of women (22%) in the Aerobics Center Longitudinal Study (ACLS) and a very low number  
9 of hypercholesterolemia cases in women ( $n < 10$ ) in several main resistance exercise  
10 categories, which prevented us from running meaningful analyses due to low statistical  
11 power. This study used data from the ACLS, which is a cohort examining the associations of  
12 clinical and lifestyle factors including PA with the development of chronic diseases and  
13 mortality. Participants received extensive preventive medical examinations at the Cooper  
14 Clinic in Dallas, Texas between January 1, 1987, and December 31, 2006. The study  
15 population consisted predominantly of non-Hispanic whites (>95%), well educated, and  
16 employed in, or retired from, professional or executive positions.<sup>16</sup> The study was annually  
17 approved by the Cooper Institute institutional review board. Before data collection at baseline  
18 and during follow-up examinations, written informed consents were acquired from each  
19 participant.

20

### 21 *Clinical examination*

22 Comprehensive medical examinations were performed at baseline. Body mass index (BMI)  
23 was calculated using measured weight and height squared ( $\text{kg}/\text{m}^2$ ). After at least 12-hour  
24 fasting, blood was sampled by a trained phlebotomist for determination of total cholesterol  
25 (mg/dl) using a basic lipid panel and via automated bioassays in the Cooper Clinic laboratory

1 in accordance with the Centers for Disease Control and Prevention Lipid Standardization  
2 Program. Resting systolic and diastolic blood pressure (mm Hg) were calculated as the  
3 average of at least two readings after 5 minutes of seated rest using the standard auscultatory  
4 methods. A medical history questionnaire was used to assess age, gender, smoking status,  
5 alcohol consumption, personal history of physician-diagnosed hypercholesterolemia, cancer  
6 and CVD, and parental history of hypercholesterolemia. More than 14 alcoholic drinks per  
7 week were defined as heavy alcohol drinking in men. <sup>11</sup>

8

### 9 *Assessment of resistance and aerobic exercise*

10 Self-reported muscle-strengthening activities, using either free weights or weight training,  
11 were collected at baseline by a PA questionnaire. Participants were queried about the weekly  
12 frequency and average exercise duration (minutes) in each session over the past 3 months. We  
13 multiplied the frequency with the average minutes per session to calculate the total amount of  
14 resistance exercise per week (minutes/week). Frequency (0, 1, 2, 3, 4 or  $\geq 5$  times/week) and  
15 total amount (0, 1-59, 60-119, 120-179 and  $\geq 180$  minutes/week) of resistance exercise, as  
16 well as meeting the 2008 Physical Activity Guidelines for resistance exercise ( $\geq 2$  times per  
17 week <sup>17</sup>) were used as our main exposures. To examine whether frequency (1-2 vs.  $\geq 3$   
18 times/week) at the same total amount of resistance exercise affects the risk of  
19 hypercholesterolemia, we combined the categories of minutes per week of resistance exercise  
20 with frequencies per week of resistance exercise. For instance, some individuals performed  
21 resistance exercise for 1 hour in 1 or 2 sessions per week (e.g., weekend warriors), while  
22 others performed the same hour of resistance exercise in 3 or more sessions per week.  
23 Aerobic exercise was determined by a PA questionnaire containing self-reported leisure-time  
24 or recreational activities over the past 3 months. Subsequently, aerobic exercise was divided  
25 into four different categories: “inactive (0 MET-minutes/week)”, “insufficient (1–499 MET-



1 minutes/week)", "medium (500-999 MET-minutes/week)" and "high ( $\geq 1,000$  MET-  
2 minutes/week)" based on the 2008 US Physical Activity Guidelines. Meeting the 2008  
3 Physical Activity Guidelines for aerobic exercise were defined as  $\geq 500$  MET-minutes/week  
4 (equivalent to  $\geq 150$  minutes of moderate-intensity activities/week) based on the guidelines.<sup>17</sup>

#### 6 *Definition of hypercholesterolemia*

7 The criteria of the National Cholesterol Education Program Adult Treatment Panel III were  
8 used to classify hypercholesterolemia.<sup>18</sup> Hypercholesterolemia was defined as total  
9 cholesterol concentration of  $\geq 240$  mg/dL or physician-diagnosed hypercholesterolemia.  
10 Participants were followed from the baseline examination to the first event or diagnosis of  
11 hypercholesterolemia for men who developed hypercholesterolemia, or the last follow-up  
12 examination through 2006 for men who did not develop hypercholesterolemia.

#### 14 *Statistical Analysis*

15 We described baseline characteristics by the total weekly amount of resistance exercise  
16 (minutes/week). Differences in baseline characteristics for participants across different  
17 amounts of resistance exercise were evaluated using the analysis of variance (ANOVA) for  
18 continuous variables and chi-squared test for categorical variables. We used Cox proportional  
19 hazard regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of  
20 incident hypercholesterolemia across different strata of weekly amounts of resistance  
21 exercise. Participants who were not engaged in resistance exercise were used as the reference  
22 category. The first regression model was adjusted for age (years) and examination year  
23 (years). The second model was adjusted for variables in model 1 plus BMI ( $\text{kg/m}^2$ ), current  
24 smoking (yes/no), heavy alcohol drinking (yes/no), abnormal electrocardiography (yes/no),  
25 systolic and diastolic blood pressure and parental history of hypercholesterolemia at baseline

1 (yes/no). The third model was adjusted for variables in model 2 plus aerobic exercise  
2 (inactive, insufficient, medium, and high) at baseline. In order to assess the independent and  
3 combined effects of resistance and aerobic exercise, we compared individuals meeting both  
4 aerobic and resistance exercise guidelines, and those meeting only aerobic or resistance  
5 exercise guidelines with those who met neither guideline. Further, to illustrate the nature of  
6 the possible dose-response relationship between resistance exercise (minutes/week) and  
7 hypercholesterolemia, we used restricted cubic spline regression. We tested 3, 4 and 5 knots  
8 and calculated the Akaike Information Criterion (AIC) to identify the best fit model.<sup>19</sup> All  
9 models had a similar AIC, and we chose the model with 5 knots, which is in line with the  
10 categorical analyses. The knots were placed at 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, and 95<sup>th</sup> percentile based on  
11 men who were participating in resistance exercise.<sup>19,20</sup> This analysis was adjusted for the  
12 covariates of model 3. We performed a test for non-linearity, which compared models with  
13 the cubic spline terms and models with only the linear terms using the likelihood ratio test.  
14 Significance was set at 2-tailed alpha <.05. All analyses were conducted using SAS software,  
15 version 9.4.

16

## 17 **Results**

18 After a median (interquartile range) follow-up of 4 years (2 to 7), 1,432 men (20%) developed  
19 hypercholesterolemia. Among men who participated in resistance exercise, most men (62%)  
20 performed resistance exercise for less than 2 hours per week (Table 1). Compared to men with  
21 no resistance exercise, men with higher levels of resistance exercise were more likely to be  
22 younger, had a lower BMI, and were more aerobically active. In addition, participants  
23 performing resistance exercise had a slightly higher prevalence of paternal history of  
24 hypercholesterolemia and lower baseline values for total cholesterol.

25

1 Men performing any resistance exercise had a 14% lower risk of developing  
2 hypercholesterolemia (HR, 0.86; 95% CI, 0.76-0.98;  $P=.02$ ) after adjustment for potential  
3 confounders including aerobic exercise levels (Table 2). Similar hypercholesterolemia risk  
4 reduction by 13% (HR, 0.87; 95% CI, 0.76- 0.99;  $P=.04$ ) was also found in men meeting the  
5 resistance exercise guidelines after full adjustment. We found that only less than one hour per  
6 week of resistance exercise was significantly associated with a 32% reduced risk of  
7 hypercholesterolemia (HR, 0.68; 95% CI, 0.54- 0.86;  $P=.001$ ) after full adjustment (model 3).  
8 Also, 2 times per week of resistance exercise was beneficial in reducing 31% risk of  
9 developing hypercholesterolemia (HR, 0.69; 95% CI, 0.54-0.88;  $P=.003$ ), compared to no  
10 resistance exercise (model 3). After further adjustment for baseline levels of total cholesterol  
11 in additional analysis, results were similar and less than one hour of weekly resistance  
12 exercise remained significant for reducing the risk of hypercholesterolemia (HR, 0.73; 95%  
13 CI, 0.58-0.93;  $P=0.01$ ). When we also adjusted for a borderline hypercholesterolemia (yes or  
14 no) at baseline defined as a total cholesterol level of 200-239 mg/dl,<sup>21</sup> we also observed a  
15 similar result (HR, 0.69; 95% CI, 0.54-0.87;  $P=.003$ ). Additional subgroup analyses for  
16 different age (<50 vs.  $\geq 50$  years old) and BMI (<25 vs.  $\geq 25$  kg/m<sup>2</sup>) groups, and men who  
17 participated in resistance exercise less than one year vs. more than one year demonstrated  
18 similar negative associations.

19  
20 Figure 1 showed that the risk of hypercholesterolemia in those performing less than one hour  
21 of weekly resistance exercise in 1-2 times per week was 42% significantly lower, compared to  
22 no resistance exercise (HR, 0.58; 95% CI, 0.42-0.81;  $P=.001$ ). However, we observed no  
23 significant results in other categories of resistance exercise. The combined effects of  
24 resistance and aerobic exercise are presented in Figure 2. The result demonstrates that  
25 meeting both guidelines for resistance and aerobic exercise was associated with the lowest

1 risk (22%) of developing hypercholesterolemia (HR, 0.78; 95% CI, 0.68-0.91;  $P=.002$ ),  
2 compared to meeting none of the guidelines. We tested effect modification by aerobic  
3 exercise on the association between resistance exercise and incident hypercholesterolemia  
4 using both interaction terms in the regression and by comparing risk estimates in the stratified  
5 analysis by meeting the aerobic exercise guidelines. We found no significant interaction  
6 ( $P>.05$ ), and the associations were similar in both individuals meeting and not meeting the  
7 aerobic exercise guidelines. Figure 3 displays the dose-response relationship between  
8 resistance exercise (minutes/week) and the risk of hypercholesterolemia. The  $P$ -value for non-  
9 linearity was not statistically significant ( $P=.13$ ), which suggest a linear dose-response  
10 relationship. However, the lowest risk of hypercholesterolemia was found at 58 minutes per  
11 week of resistance exercise (HR, 0.77; 95% CI, 0.62-0.95;  $P<.05$ ). This finding is consistent  
12 with the results in the categorical analyses (Table 2), suggesting the lowest risk of  
13 hypercholesterolemia in 1-59 minutes/week and 2 times/week of resistance exercise.

14

## 15 **Discussion**

16 This study showed that less than one hour of weekly resistance exercise, even 1-2 times per  
17 week, was associated with significantly lower risk of developing hypercholesterolemia,  
18 compared to no resistance exercise, whereas no benefits were found at higher levels of  
19 resistance exercise. In addition, meeting both resistance and aerobic exercise guidelines  
20 yielded the largest benefits with a 21% lower risk in developing hypercholesterolemia,  
21 compared to meeting none of the guidelines. This result suggests that adding relatively small  
22 doses of resistance exercise (<1 hour/week) to aerobic exercise could provide additional  
23 benefits in preventing hypercholesterolemia.

24

1 Several recent meta-analyses of controlled exercise trials found inconsistent results regarding  
2 the effect of resistance exercise training on total cholesterol levels.<sup>12-14</sup> The lack of  
3 improvement in total cholesterol in several intervention studies might be due to short exercise  
4 intervention periods, lack of statistical power because of small sample sizes and low total  
5 cholesterol values at baseline in relatively healthy populations, which may reduce the  
6 potential effects of resistance exercise.<sup>11</sup> However, our large prospective study with a long-  
7 term follow-up clearly demonstrates that engagement in resistance exercise is significantly  
8 associated with a lower risk of incident hypercholesterolemia. This result is consistent with  
9 the findings from the earlier cross-sectional analysis by Drenowatz et al.<sup>15</sup> However, the  
10 current study further investigated the prospective effect of meeting the resistance exercise  
11 guidelines, independent of and combined with aerobic exercise, and the dose-response  
12 relationship between resistance exercise and the incidence of hypercholesterolemia.

13  
14 Although the current PA guidelines suggest that more exercise and physical activity generally  
15 provide greater health benefits, the dose-response relationships of different types and  
16 intensities of exercise with different health outcomes are still unclear and controversial.<sup>22, 23</sup>  
17 Therefore, we investigated the dose-response relationship between resistance exercise and the  
18 risk of hypercholesterolemia in this study. First, in the association between exercise frequency  
19 and hypercholesterolemia, we found that 2 times per week of resistance exercise was  
20 associated with a lower risk of developing hypercholesterolemia. However, higher  
21 frequencies of resistance exercise were not necessary to produce additional benefits to prevent  
22 hypercholesterolemia (Table 2). The limitation of using frequency of exercise is that it does  
23 not fully reflect the total amount of exercise, since exercise duration in each session is not  
24 considered in frequency of exercise. Therefore, we also used the total volume (minutes) of  
25 resistance exercise, and found a significantly lower risk of developing hypercholesterolemia

1 in less than one hour per week. However, the benefits to prevent hypercholesterolemia with  
2 higher amounts of resistance exercise were not significant ( $P >.05$ ), compared to no resistance  
3 exercise, which again suggests no further benefits by performing more resistance exercise. In  
4 fact, the associations between frequency and total amount of weekly resistance exercise and  
5 hypercholesterolemia were more likely reverse J- or U-shaped with a quadratic trend rather  
6 than linear trend (Table 2). When using the restricted cubic spline regression (Figure 3), the  
7  $P$ -value for non-linearity suggested a linear dose-response relationship. However, we found  
8 the largest benefit at 58 minutes/week of resistance exercise (HR, 0.77; 95% CI, 0.62-0.95),  
9 similar to the result from the categorical data analyses in Table 2. Further, HRs for higher  
10 levels of resistance exercise were directed towards 1.00. Nevertheless, these results should be  
11 interpret carefully, since the CIs are wide and sample size are smaller at higher dose of  
12 resistance exercise. A recent study investigating the association between resistance exercise  
13 and CVD in women also found no additional benefits in higher levels of resistance exercise.  
14 However, they found a significant effect of resistance exercise in 60-119 minutes per week,  
15 which is a higher amount of resistance exercise (minutes/week) than what we found.<sup>24</sup> An  
16 earlier study investigating the associations between muscular strength and CVD and all-cause  
17 mortality also found no additional benefits in the highest third, compared to the middle third  
18 of muscular strength in a similar population.<sup>25</sup> Nevertheless, other studies examining CVD  
19 risk factors such as diabetes did show a linear dose-response relationship with larger benefits  
20 by participating in more resistance exercise.<sup>26, 27</sup> The difference might be explained by  
21 different dose-response curves of resistance exercise with hypercholesterolemia and diabetes,  
22 possibly related with the improvements in insulin sensitivity noted with resistance exercise in  
23 patients with marked insulin resistance, such as those with diabetes mellitus. These  
24 contradicting findings suggest that further studies focussing on the dose-response relationship  
25 between resistance exercise and different health outcomes are needed to identify the optimal

1 amount of resistance exercise and whether there exists an upper limit for various health  
2 outcomes.

3

4 Whether a lower frequency of resistance exercise provides health benefits is important from a  
5 public health perspective, since lack of time is a common barrier to perform exercise.<sup>28</sup> For  
6 example, some people may prefer 1 hour of resistance exercise in 1-2 sessions per week,  
7 whereas others prefer to divide the same hour of weekly resistance exercise in more than 2  
8 sessions. A recent observational study demonstrated that individuals who met the aerobic  
9 activity guidelines by performing their activities in only 1-2 days per week (weekend  
10 warriors) had a similar lower risk of CVD and mortality as regularly active individuals,  
11 compared to inactive individuals.<sup>29</sup> These findings align with our data, where we did not find  
12 a difference in risk estimates for different frequencies (1-2 vs.  $\geq 3$  sessions/week) at the same  
13 amount of resistance exercise (Figure 1). This result suggests that even a small amount of  
14 resistance exercise at a low frequency may provide maximal benefits to prevent  
15 hypercholesterolemia. This finding could motivate more people to start participating in  
16 relatively low doses of resistance exercise for health benefits and makes performing resistance  
17 exercise more feasible at population levels.

18

19 There are some limitations in our study. We examined a large population for a relatively long  
20 follow-up period, but this cohort included primarily well-educated non-Hispanic white men  
21 from middle-to-upper socio-economic strata. This may limit the generalizability of the results  
22 to other populations. Also, the findings from this study apply only to men. However,  
23 physiological characteristics including total cholesterol value of this cohort were comparable  
24 to other representative population samples although ACLS participants were slightly more  
25 active and leaner.<sup>16</sup> Second, this study used self-reported data on aerobic and resistance

1 exercise, which may cause measurement errors due to over-reporting of leisure-time physical  
2 activity in general.<sup>30</sup> Nevertheless, over-reporting generally induces an underestimation of  
3 the true effect of resistance exercise on the incidence of hypercholesterolemia.<sup>31</sup> Also, we  
4 only took baseline levels of PA into account for the analyses, therefore changes in PA patterns  
5 over time were not included in the study. However, subgroup analyses for men who  
6 participated in resistance exercise less than one year vs. more than one year at baseline  
7 demonstrated similar negative associations with incident hypercholesterolemia. Third, we had  
8 no information about lipid-lowering medication or health-promoting drugs that affect the  
9 cholesterol level. However, we excluded participants with a history of CVD and  
10 hypercholesterolemia at baseline. Finally, cholesterol levels could be affected by diet and  
11 sedentary lifestyle, but information on diet and sedentary lifestyle was lacking in this cohort.  
12 Since diet and sedentary lifestyle might be possible confounders in the association between  
13 resistance exercise and hypercholesterolemia, future studies should take diet and sedentary  
14 lifestyle into account to see whether the association is affected. Also, future investigations  
15 should explore the type/nature (e.g., intensity, isolated, circuit, etc.) of resistance exercise on  
16 hypercholesterolemia outcomes. Further, randomized controlled trials of resistance exercise  
17 are necessary to examine the causality and dose-response effects of resistance exercise on  
18 hypercholesterolemia in the future. Despite these limitations, this is the first study, to our  
19 knowledge, that has investigated the dose-response relationship between resistance exercise  
20 and incident hypercholesterolemia in a large population. In addition, we conducted more  
21 comprehensive analyses using both weekly frequency and total amount of resistance exercise,  
22 and the effects of meeting the current resistance exercise guidelines, independent of and  
23 combined with meeting the aerobic exercise guidelines.

24

## 25 **Conclusion**



1 Compared to no resistance exercise, men performing resistance exercise less than 1 hour per  
2 week, which could be easily accomplished by most adults, is significantly associated with the  
3 lowest risk of hypercholesterolemia, independent of aerobic exercise. However, the lowest  
4 risk of hypercholesterolemia was found at 58 minutes per week of resistance exercise based  
5 on restricted cubic spline regression (Figure 3). Meeting both recommended resistance and  
6 aerobic exercise guidelines provides the highest additional health benefit in the prevention of  
7 hypercholesterolemia. Therefore, our results suggest that resistance exercise, combined with  
8 aerobic exercise, could be encouraged in order to reduce the risk for developing  
9 hypercholesterolemia and further CVD in men. This supports the current PA guidelines and  
10 could have profound impact from a population and public health perspectives. However,  
11 future studies with a more rigorous analysis including significant potential confounders (e.g.,  
12 diet, medications) are needed to produce more reliable and unbiased results.

13

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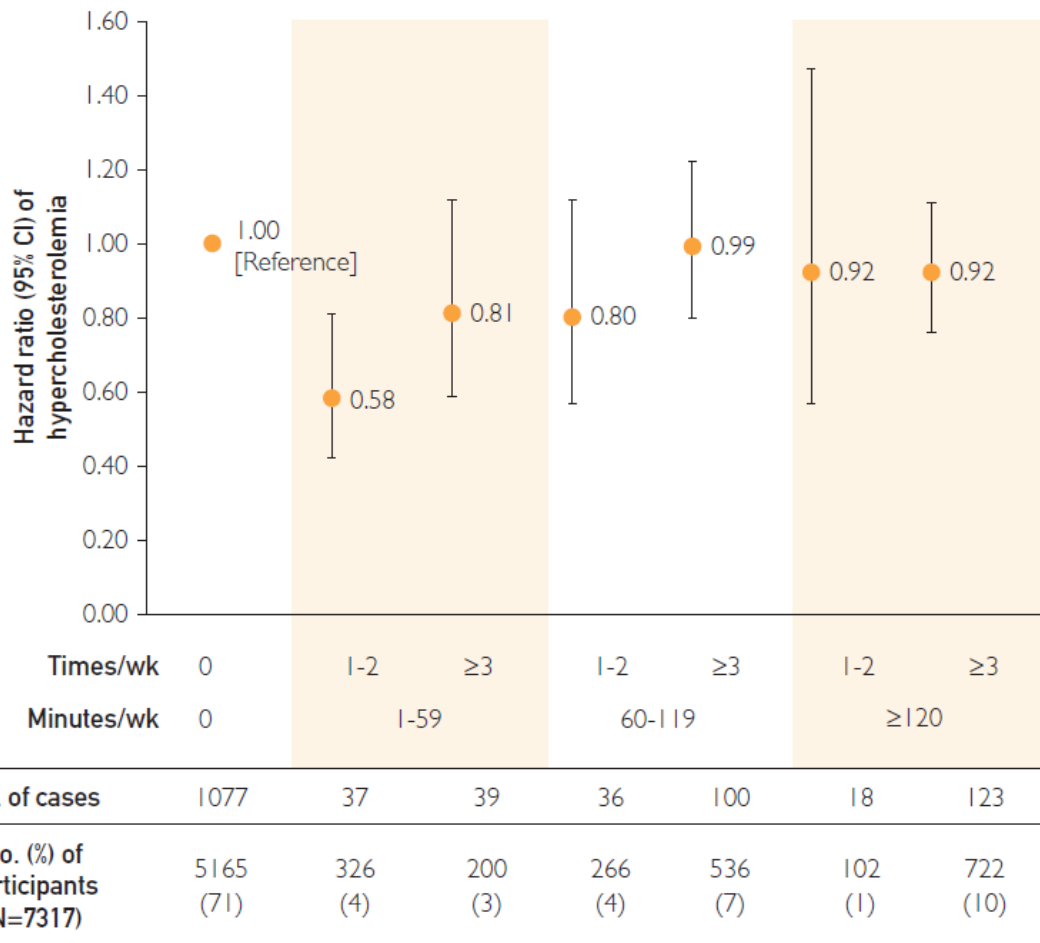
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1 **Figure legends**



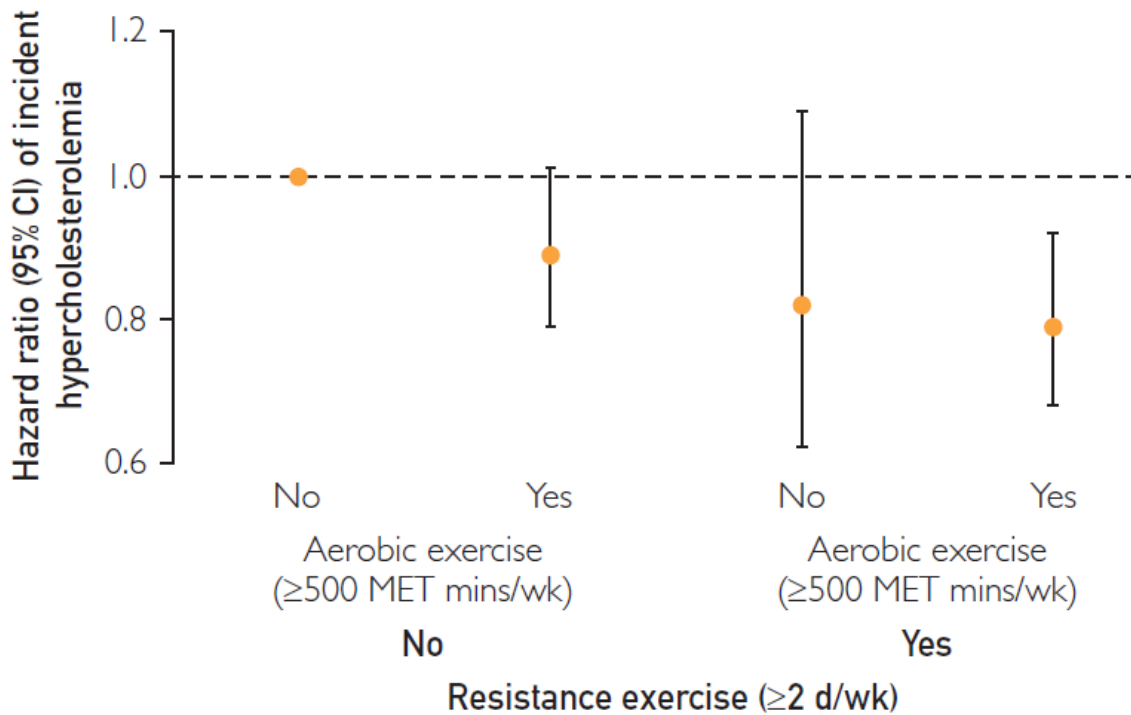
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3 **Figure 1.** Hazard ratios of hypercholesterolemia by the combination of weekly frequency (1-2  
4 vs.  $\geq 3$  times/week) and minutes of resistance exercise (0, 1-59, 60-119, and  $\geq 120$  min/week).

5 The dots indicate hazard ratios and the bars indicate 95% confidence intervals. The model  
6 was adjusted for age, examination year, body mass index, current smoking, heavy alcohol  
7 drinking, abnormal electrocardiography, systolic and diastolic blood pressure, parental history  
8 of hypercholesterolemia, and aerobic exercise.

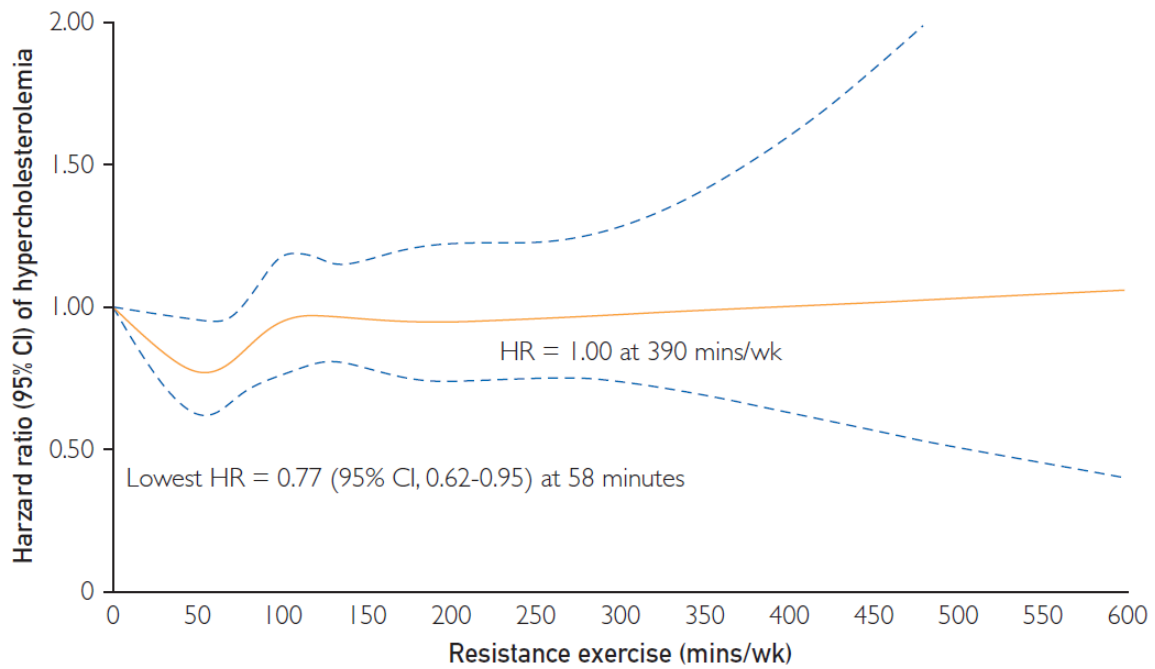
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**Figure 2.** Hazard ratios of hypercholesterolemia by meeting the 2008 US Physical Activity Guidelines for resistance ( $\geq 2$  days/week) and aerobic activities ( $\geq 500$  MET-minutes/week). The dots present hazard ratios and the bars 95% confidence intervals. The hazard ratio (95% CI) was 0.89 (95% CI, 0.79-1.01) for only meeting the aerobic exercise guidelines, 0.82 (95% CI, 0.62-1.09) for only meeting the resistance exercise guidelines, and 0.79 (95% CI, 0.68-0.91) for meeting both guidelines. The model was adjusted for age, examination year, body mass index, current smoking, heavy alcohol drinking, abnormal electrocardiography, systolic and diastolic blood pressure, and parental history of hypercholesterolemia.



1

2 **Figure 3.** The dose-response relationship between resistance exercise (minutes/week) and the

3 risk of hypercholesterolemia. Dotted lines represent 95% confidence intervals for the trend

4 obtained from restricted cubic spline regression (5 knots at 25, 60, 90, 135 and 270

5 minutes/week). The model included the following covariates: age, examination year, body

6 mass index, current smoking, heavy alcohol drinking, abnormal electrocardiography, systolic

7 and diastolic blood pressure, parental history of hypercholesterolemia, and aerobic exercise.

8  $P=.13$  for a nonlinear relationship.



**Table 1.** Baseline characteristics of the 7,317 men by weekly minutes of resistance exercise <sup>a,b</sup>.

Characteristics	Weekly minutes of resistance exercise (min/week)					P-value
	0 (n=5,165)	1-59 (n=526)	60-119 (n=802)	120-179 (n=378)	≥180 (n=446)	
Age (years)	47 (10)	45 (9)	46 (9)	45 (10)	42 (10)	<.001
BMI (kg/m <sup>2</sup> )	26.5 (3.8)	25.7 (3.1)	25.6 (3.0)	26.1 (3.2)	25.9 (3.5)	<.001
Current smokers	674 (13%)	52 (10%)	81 (10%)	49 (13%)	53 (12%)	.06
Heavy alcohol drinking	490 (9%)	53 (10%)	77 (10%)	36 (10%)	32 (7%)	.56
Aerobic exercise (MET-min/week)						<.001
0	1,659 (32%)	30 (6%)	32 (4%)	24 (6%)	35 (8%)	
1-499	771 (15%)	66 (13%)	87 (11%)	52 (14%)	56 (13%)	
500-999	881 (17%)	121 (23%)	191 (24%)	72 (19%)	73 (16%)	
≥ 1000	1,854 (36%)	309 (59%)	492 (61%)	230 (61%)	282 (63%)	
Abnormal ECG	407 (8%)	42 (8%)	61 (8%)	22 (6%)	25 (6%)	.30
Parental history of hypercholesterolemia	99 (2%)	13 (2%)	32 (4%)	16 (4%)	15 (3%)	<.001
Systolic blood pressure (mmHg)	121 (13)	121 (13)	121 (13)	121 (12)	122 (13)	.37
Diastolic blood pressure (mmHg)	81 (10)	80 (9)	80 (9)	81 (9)	81 (9)	.06
Total cholesterol (mg/dl)	194.6 (26.6)	190.1 (26.8)	188.5 (27.6)	188.4 (29.1)	185.1 (29.0)	<.001

<sup>a</sup> BMI=body mass index; ECG=electrocardiographic findings; MET=metabolic

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equivalent task.

<sup>b</sup>Data is presented in mean (SD) unless indicated as n (%).

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**Table 2.** Hazard ratio of hypercholesterolemia by weekly frequency and minutes of resistance exercise.

	N (%)	No. of cases	Adjusted Hazard Ratio		
			Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>
<b>Weekly minutes of resistance exercise (min/week)</b>					
0	5,165 (71%)	1,077	1.00 [reference]	1.00 [reference]	1.00 [reference]
1-59	526 (7%)	76	0.65 (0.51-0.82)	0.66 (0.52-0.83)	0.68 (0.54-0.86)
60-119	802 (11%)	136	0.88 (0.73-1.05)	0.91 (0.76-1.08)	0.93 (0.78-1.12)
120-179	378 (5%)	64	0.81 (0.63-1.05)	0.83 (0.65-1.07)	0.86 (0.67-1.11)
≥180	446 (6%)	77	0.94 (0.74-1.18)	0.95 (0.75-1.20)	0.98 (0.77-1.24)
P for linear trend			.04	.10	.28
P for quadratic trends			.02	.04	.08
<b>Any resistance exercise</b>					
No (0 min/week)	5,165 (71%)	1,077	1.00 [reference]	1.00 [reference]	1.00 [reference]
Yes (≥1 min/week)	2,152 (29%)	353	0.81 (0.72-0.92)	0.83 (0.74-0.94)	0.86 (0.76-0.98)
<b>Weekly frequency of resistance exercise (times/week)</b>					
0	5,165 (71%)	1,077	1.00 [reference]	1.00 [reference]	1.00 [reference]
1	165 (2%)	20	0.74 (0.47-1.15)	0.75 (0.48-1.18)	0.77 (0.49-1.20)
2	529 (7%)	71	0.66 (0.51-0.83)	0.67 (0.53-0.85)	0.69 (0.54-0.88)
3	951 (13%)	171	0.89 (0.75-1.04)	0.91 (0.77-1.07)	0.93 (0.79-1.10)
4	304 (4%)	50	0.78 (0.59-1.04)	0.81 (0.61-1.08)	0.84 (0.63-1.12)
≥ 5	203 (3%)	41	0.96 (0.70-1.32)	0.99 (0.72-1.35)	1.02 (0.74-1.39)
P for linear trend			.01	.04	.13

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<i>P</i> for quadratic trends			.02	0.02	.04
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**Recommended resistance exercise**

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No (<2 days/week)	5,330 (73%)	1,097	1.00 [reference]	1.00 [reference]	1.00 [reference]
Yes (≥2 days/week)	1,987 (27%)	333	0.82 (0.73-0.93)	0.84 (0.74-0.96)	0.87 (0.76-0.99)

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<sup>a</sup> Adjusted for age and examination year.

<sup>b</sup> Adjusted for model 1 plus body mass index, current smoking, heavy alcohol drinking, abnormal electrocardiography, systolic and diastolic blood pressure, and parental history of hypercholesterolemia.

<sup>c</sup> Adjusted for model 2 plus aerobic exercise (inactive, insufficient, medium, and high)

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