REVIEW ARTICLE

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

A Meta-analysis

Satoru Kodama, MD; Shiro Tanaka, MS; Kazumi Saito, MD; Miao Shu, MS; Yasuko Sone, MS; Fumiko Onitake, MS, RD; Emiko Suzuki, PhD; Hitoshi Shimano, MD, PhD; Shigeru Yamamoto, PhD, RD; Kazuo Kondo, MD, PhD; Yasuo Ohashi, PhD; Nobuhiro Yamada, MD, PhD; Hirohito Sone, MD, PhD

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]; $P<.001$). 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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Author Affiliations:
Department of Lifestyle Medicine and Nutritional Sciences, Ochanomizu University, Tokyo, Japan (Drs Kodama, Saito, Suzuki, Yamamoto, Kondo, and H. Sone and Mss Shu, Y. Sone, and Onitake); Departments of Sports Medicine and Health Sciences (Dr Kodama, Saito, Yamada, and H. Sone and Ms Shu) and Internal Medicine (Drs Kodama, Saito, Shimano, and H. Sone and Ms Shu), University of Tsukuba, Tsukuba, Japan; and Department of Biostatistics, Epidemiology, and Preventive Health Sciences, University of Tokyo (Mr Tanaka and Dr Ohashi).

CARDIOVASCULAR DISEASE (CVD) is the leading cause of death worldwide.[1] Low blood levels of high-density lipoprotein cholesterol (HDL-C) are an independent risk factor for CVD.[2,3] Cross-sectional data provide strong evidence that people who are more physically active have higher HDL-C levels.[4-6] Thus, the value of regular aerobic exercise in increasing serum HDL-C level and in reducing the risk of CVD has received widespread acceptance.[7] 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.[8] 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

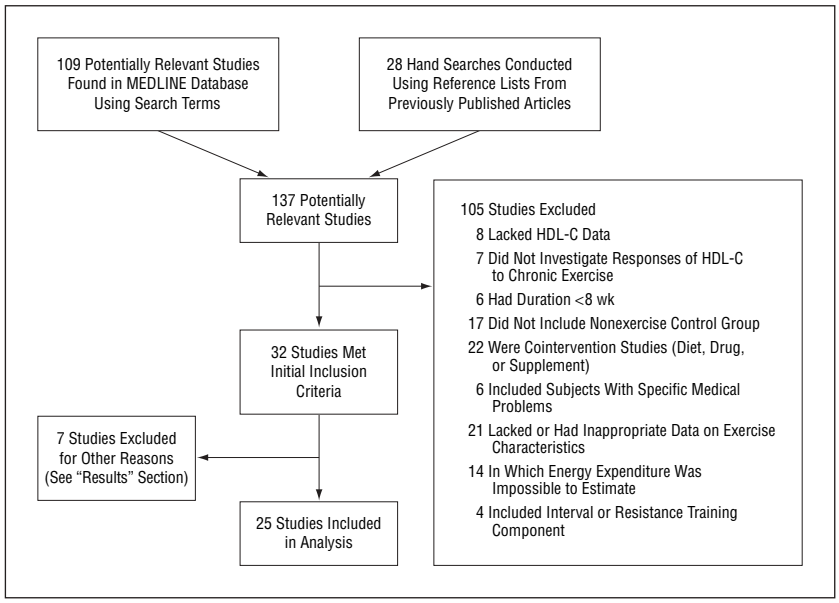

Figure 1. Selection of articles on randomized controlled trials for meta-analysis of exercise and its effects on high-density lipoprotein cholesterol (HDL-C) level.

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] Cointervention 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 studies[10-23] 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 ($\dot{V}O_2$max or $\dot{V}O_2$peak) (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.[28,29] Absolute intensity was calculated by multiplying relative intensity, ie, percentage of $\dot{V}O_2$peak or $\dot{V}O_2$max, 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 al[34] as follows:

$$SE = \sqrt{(SE_{Baseline})^2 + (SE_{Follow\text{-}up})^2 - 2 \times 0.5 \times (SE_{Baseline}) \times (SE_{Follow\text{-}up})}.$$

Each MDHC was weighted according to the inverse of its variance and the average. Weighted MDHCs were pooled with a random-effects model[35] (ie, pooled MDHC). The χ^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.[36,37]

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

Source	Age, y	Sex, % M	Ex-n (Pre–Ex-n*)	C-n	HDL-C, mg/dL	TC, mg/dL	TG, mg/dL	BF, %	BMI	Max Cap†
Aldred et al,[30] 1995	49	0	11 (13)	13	61	207	77	ND	ND	39.7
Baker et al,[45] 1986	59	100	20 (23)	15	36	230	89	27.1	ND	30.6
Busby et al,[46] 1985	50	0	12	12	50	173	71	ND	22.6	23.6
Cunningham et al,[47] 1987	63	100	100 (113)	100	45	229	55	ND	26.2	30.0
Duncan et al,[32] 1991	20-40	0	16 (25)	10	54	180	78	29.3	23.8	30.4
			12 (26)	10	57	185	79	28.9	24.5	31.0
			18 (26)	10	53	184	90	29.4	23.8	31.1
Fahlman et al,[48] 2002	75	0	15	15	44	182	128	ND	26.0	18.5
Grandjean et al,[49] 1996	ND	0	20	17	56	203	133	28.1	ND	28.5
Houmard et al,[50] 1994	48	100	13 (18)	7	35	200	155	28.2	30.4	29.5
Huttunen et al,[51] 1979	43	100	44 (50)	46	48	263	131	ND	ND	43.5
Juneau et al,[52] 1987	49	100	29 (30)	28	46	225	143	21.2	ND	32.5
	47	0	28 (30)	28	63	216	90	28.1	ND	26.2
Kokkinos et al,[53] 1998	58	100	15 (17)	19	45	220	130	ND	30.6	21.0
Kraus et al,[54] 2002	52	64	19	26	42	200	159	ND	29.1	29.5
	51	56	17	26	44	204	131	ND	29.2	28.9
	52	54	22	26	43	204	148	ND	29.2	28.3
Kukkonen-Harjula et al,[55] 1998	41	100	53 (58)	55	50	205	103	24.1	25.5	40.0
Lindheim et al,[56] 1994	50	0	25	20	63	217	82	ND	ND	27.5
Nieman et al,[57] 2002	45	0	21	22	44	207	142	43.3	32.6	22.4
Ready et al,[58] 1995	61	0	15 (19)	10	50	258	157	30.7	30.5	25.5
Santiago et al,[59] 1995	31	0	16	11	64	184	73	28.2	24.2	32.8
Sopko et al,[60] 1985	32	100	9	8	39	174	124	30.2	ND	30.0
Stensel et al,[31] 1993	51	100	42 (48)	23	54	220	93	29.2	25.2	35.7
Sunami et al,[61] 1999	67	50	20	20	51	205	96	21.1	22.4	30.2
Thomas et al,[62] 1984	18-32	100	5	6	39	175	82	13.8	ND	56.0
		100	7	6	40	171	83	12.8	ND	54.5
		0	9	6	44	173	81	21.8	ND	41.3
		0	11	6	40	167	80	27.9	ND	39.3
Thomas et al,[63] 1985	23	100	11	8	49	161	ND	ND	ND	50.0
Wood et al,[64] 1983	46	100	46 (48)	33	49	214	119	21.6	24.9	34.9
Woolf-May et al,[65] 1998	57	100	10	10	55	221	114	ND	25.8	30.7
	54	0	6	5	78	222	115	ND	24.2	29.3
Woolf-May et al,[66] 1999	55	100	5	4	45	224	121	ND	26.3	34.3
	51	0	13	8	62	224	122	ND	26.6	26.4

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.

pooled data. Missing data were input by means of a regression model if needed; BMI was regressed by percentage of men and body mass, and percentage of body fat was regressed by percentage of men, body mass, and maximal aerobic capacity. A $P<.05$ was considered statistically significant. All analyses were performed with SPSS statistical software (version 14.0; SPSS Inc, Chicago, Ill).

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,[38-41] 1 was excluded because of poor compliance (<60% adherence to the program),[42] and 2 were excluded because of a crossover design in which carryover effects could not be ignored.[43,44]

Finally, 25 articles (35 trials)[30-32,45-66] 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%

*References 30-32, 45, 47, 50-53, 55, 58, 64.

†References 46, 48, 49, 54, 56, 57, 59-63, 65, 66.

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

	Exercise Intervention Characteristics							Information for Dietary Assessment	
Source	Weeks	Freq	Prescribed Exercise Intensity	D, min	Weekly EE, kcal	MET	Type of Exercise	Dietary Instruction*	Dietary Record†
Aldred et al[30]	12	6.1	Brisk walking; mean exercise intensity, 74% of HRmax	25	877	5.2	W/J	N	N
Baker et al[45]	20	3.0	65%-75% of HRR	48	1208	5.9	W/J	Y	Y
Busby et al[46]	12	3.0	70%-80% of HRmax	30	299	3.0	W/J	N	N
Cunningham et al,[47]	52	2.5	(≥60 maximal METs/10)% of HRR	32	578	5.9	W/J	N	N
Duncan et al[32]	24	5.0	Walking speed, 8.0 km/h	36	1294	6.7	W/J	Y	Y
	24	5.0	Walking speed, 6.4 km/h	45	1293	5.1	W/J	Y	Y
	24	5.0	Walking speed, 4.8 km/h	60	1166	3.6	W/J	Y	Y
Fahlman et al[48]	12	3.0	70% of HRR	50	599	3.5	W/J	Y	Y
Grandjean et al[49]	12	4.0	Progressively increased intensity (from 60%-70% of $\dot{V}O_2$max to 70%-80% of $\dot{V}O_2$max)	40	1200	5.6	O	N	N
Houmard et al[50]	14	3.8	Progressively increased intensity (from 70%-80% of HRmax to 80%-85% of HRmax) and exercise duration (30 min/session to 45 min/session)	41‡	1245	4.9	W/J	N	N
Huttunen et al[51]	16	3.0	Progressively increased intensity (from 40% of HRR to 66% of HRR) 15 min warming up; 10 min cooling down	38§	927	6.0	O	Y	N
Juneau et al[52]	24	5.0	Mean exercise intensity, 72% of HRmax	47	1725	5.3	W/J	Y	N
	24	5.0	Mean exercise intensity, 69% of HRmax	54	1175	3.9	W/J	Y	N
Kokkinos et al[53]	16	3.0	60%-80% of HRmax	44	462	2.1	C	N	N
Kraus et al[54]	26	3.4	40%-55% of $\dot{V}O_2$peak	52	920	3.3	O	Y	Y
	26	3.0	65%-80% of $\dot{V}O_2$peak	39	1003	5.6	O	Y	Y
	26	3.8	65%-80% of $\dot{V}O_2$peak	46	1423	5.4	O	Y	Y
Kukkonen-Harjula et al[55]	15	4.0	70% of $\dot{V}O_2$max	45	1742	7.6	W/J	Y	Y
Lindheim et al[56]	26	3.0	70% of HRmax	30	322	3.3	C	N	N
Nieman et al[57]	12	5.0	Progressively increased intensity (from 65%-70% of HRmax to 70%-80% of HRmax)	45	1151	3.3	W/J	N	N
Ready et al[58]	26	4.9	54% of HRR	54	1156	3.3	W/J	Y	Y
Santiago et al[59]	40	4.0	Treadmill walking, 4.8 km/session; mean exercise intensity, 72% of HRmax	50	875	3.9	W/J	N	Y
Sopko et al[60]	12	5.0	6 METs	67	3088	5.3	W/J	Y	Y
Stensel et al[31]	52	2-3	Walking speed, 1.90 m/s	28	536	5.5	W/J	N	Y
Sunami et al[61]	26	2-4	2-4 sessions/wk	60	570	3.4	C	Y	Y
Thomas et al[62]	12	3.0	75% of HRmax	42§	1330	7.8	W/J	N	N
	12	3.0	75% of HRmax	24§	664	7.7	W/J	N	N
	12	3.0	75% of HRmax	74§	1343	6.1	W/J	N	N
	12	3.0	75% of HRmax	37§	662	5.6	W/J	N	N
Thomas et al[63]	11	3.0	75%-85% of HRmax	42§	1415	8.9	W/J	N	N
Wood et al[64]	52	3-5	70%-85% of maximal aerobic capacity	28‖	1117	7.6	W/J	N	Y
Woolf-May et al[65]	18	6.0	68% of $\dot{V}O_2$max	23	828	4.2	W/J	N	N
	18	6.0	68% of $\dot{V}O_2$max	23	623	4.0	W/J	N	N
Woolf-May et al[66]	18	4.4	Approximately 70%-75% of $\dot{V}O_2$max	35	1340	6.0	W/J	Y	N
	18	4.4	Approximately 70%-75% of $\dot{V}O_2$max	35	884	4.4	W/J	Y	N

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 O_2/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; $\dot{V}O_2$max, maximal oxygen uptake; $\dot{V}O_2$peak, 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.

‖Assuming that 1 minute of warm-up corresponds to 0.5 minute of exercise training.

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.

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)[48] 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 relative or 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.[67] 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

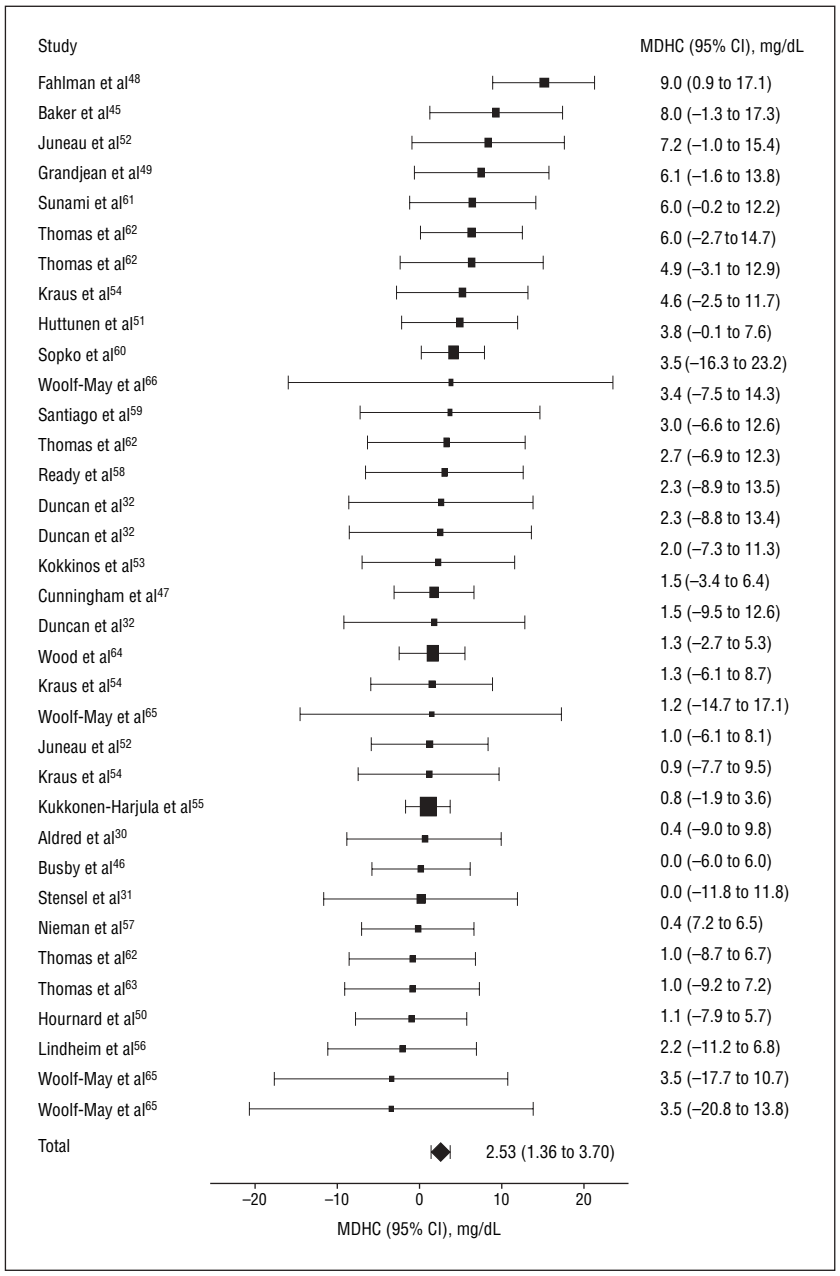

Figure 2. Mean differences in high-density lipoprotein cholesterol (HDL-C) change (MDHC) between exercise and nonexercise control groups in randomized controlled trials. The area of each square is proportional to the inverse of study variance in the analysis. Diamond indicates average net change in HDL-C level; horizontal lines indicate 95% confidence intervals (CIs). The χ^2 value for heterogeneity was 38.7 ($P=.31$) and the z score (ie, standardized mean difference) for overall effect was 4.23 ($P<.001$).

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,[68] 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, 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.[69] 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 al[70] and Halbert et al[71] 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 al[72] 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 in-

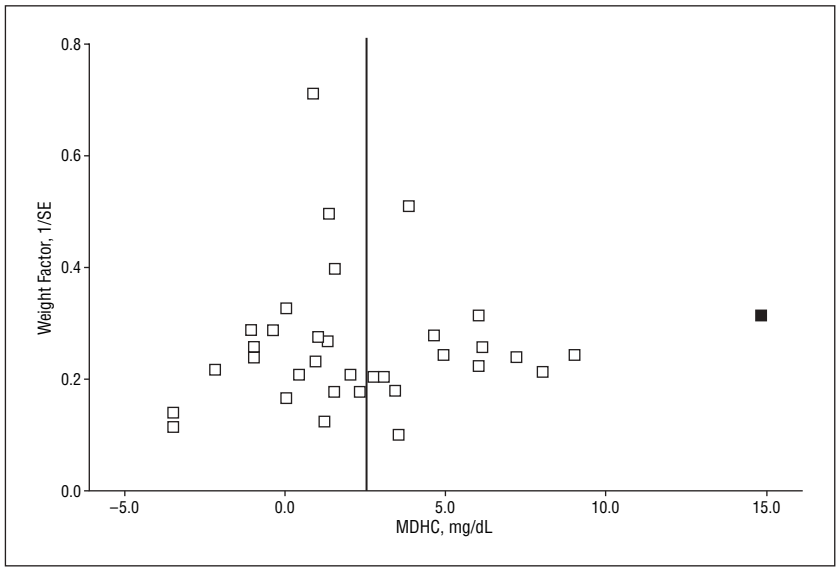

Figure 3. Funnel plot to explore publication bias in 35 randomized controlled trials of exercise and high-density lipoprotein cholesterol (HDL-C) level. Open squares represent individual trials. Mean difference in HDL-C change (MDHC) is plotted against the weight factor (reciprocal of its standard error). The funnel plot was roughly symmetrical with regard to mean effect size (vertical line), except for an outlying study,[48] which is plotted with a black square. To convert HDL-C to millimoles per liter, multiply by 0.0259.

Table 3. Test for Pooled Mean Difference in HDL-C Change Between Exercise and Control Groups Through Exercise

Variable	No. of Strata (No. of Exercisers)	*z* Score* (*P* Value)		
		Unadjusted	Adjusted 1†	Adjusted 2‡
Weekly EE, kcal/wk				
≤600	5 (114)	0.73 (.47)	0.76 (.45)	0.94 (.35)
601-900	8 (174)	0.60 (.55)	0.66 (.51)	0.56 (.58)
901-1200	9 (228)	2.15 (.03)	2.23 (.03)	1.72 (.08)
>1200	12 (204)	2.94 (.003)	2.86 (.004)	3.13 (.002)
Weekly exercise length, min/wk				
≤90	5 (186)	0.17 (.86)	0.25 (.80)	0.17 (.86)
91-120	4 (118)	1.41 (.16)	1.49 (.14)	1.21 (.23)
121-150	7 (78)	1.96 (.05)	1.93 (.05)	1.92 (.06)
>150	18 (338)	3.09 (.002)	3.04 (.002)	3.19 (.001)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; weekly EE, estimated energy expenditure per week.

*The *z* score is calculated by dividing each pooled mean difference in HDL-C change by the standard deviation.

†Adjusted for age and intervention period.

‡Adjusted for age, intervention period, sex (percentage of men), HDL-C level, and total cholesterol level.

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) effect a change in HDL-C level. Differences in controlled variables among studies, such as exercise duration and volume, could account for the varied results.[8,25,73,74] 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.[8,74]

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[67] 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 recommendation 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

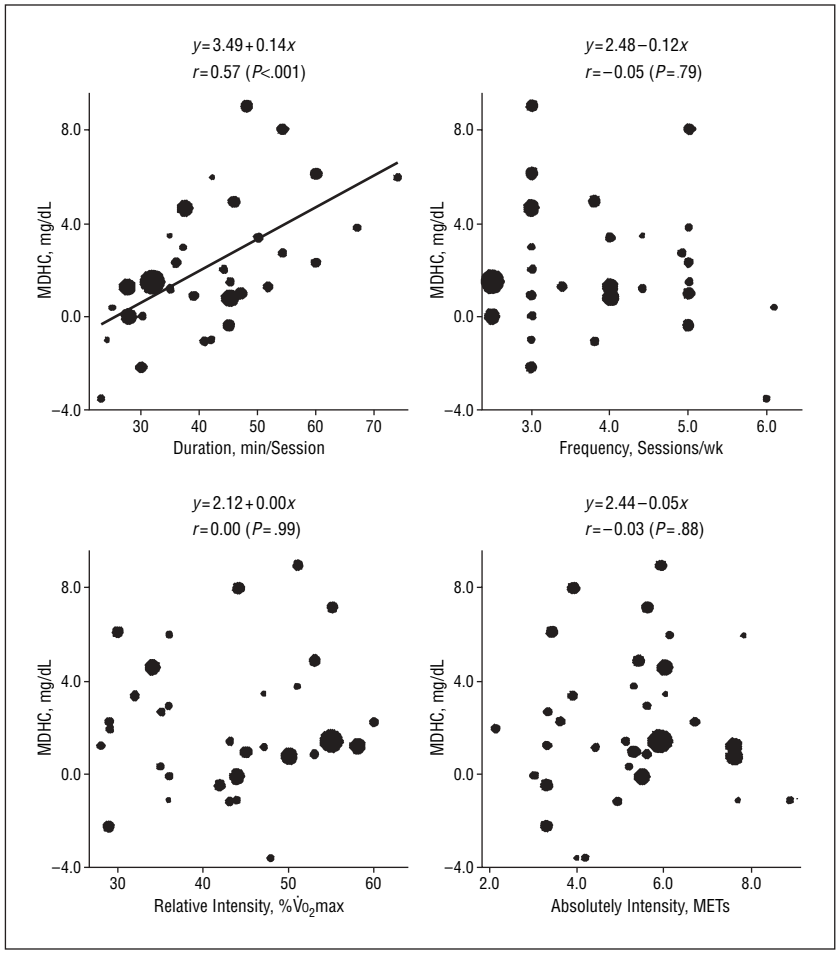

Figure 4. Associations between exercise characteristics and mean differences in high-density lipoprotein cholesterol (HDL-C) change (MDHC) between exercise and control groups. Each trial was weighted by the inverse of the sample size of each exercise group. The area of the circle is proportional to the study weight (inverse of the sample size). MET indicates absolute exercise intensity in metabolic equivalents (1 MET corresponds to 3.5 mL of O_2/kg per minute); $\dot{V}O_2$max, maximal oxygen uptake. To convert HDL-C to millimoles per liter, multiply by 0.0259.

Table 4. Relationships Between Exercise Characteristics and Mean Difference in HDL-C Change Between Exercise and Control Groups When Weekly Exercise Volume Is Controlled

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

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.

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

Model	Parameter*	Coefficient (SE)	Cumulative r^2	*P* Value
Model 1†	TC	0.04 (0.02)	0.14	.009
	Men vs women‡	−2.44 (1.12)	0.18	.04
	% BF	−0.14 (0.07)	0.28	.05
Model 2§	TC	0.05 (0.02)	0.14	.004
	BMI	0.35 (0.15)	0.26	.03

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 with percentage of BF.

‡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 men and BMI.

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 Mazaskil 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-analyses[70,71] 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 900 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 ($\geq$220 mg/dL [$\geq$5.7 mmol/L]). The mechanism for this effect should be investigated in the future.

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Correspondence: Hirohito Sone, MD, PhD, Department of Lifestyle Medicine and Nutritional Sciences, Ochanomizu University, 2-1-1 Otsuka, Bunkyo-ku, Tokyo, Japan 112-8610 (sone.hirohito@ocha.ac.jp).

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, Onitake, 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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