ORIGINAL RESEARCH

Effects of Exercise Training on Cardiorespiratory Fitness and Biomarkers of Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background—Guidelines recommend exercise for cardiovascular health, although evidence from trials linking exercise to cardiovascular health through intermediate biomarkers remains inconsistent. We performed a meta-analysis of randomized controlled trials to quantify the impact of exercise on cardiorespiratory fitness and a variety of conventional and novel cardiometabolic biomarkers in adults without cardiovascular disease.

Methods and Results—Two researchers selected 160 randomized controlled trials (7487 participants) based on literature searches of Medline, Embase, and Cochrane Central (January 1965 to March 2014). Data were extracted using a standardized protocol. A random-effects meta-analysis and systematic review was conducted to evaluate the effects of exercise interventions on cardiorespiratory fitness and circulating biomarkers. Exercise significantly raised absolute and relative cardiorespiratory fitness. Lipid profiles were improved in exercise groups, with lower levels of triglycerides and higher levels of high-density lipoprotein cholesterol and apolipoprotein A1. Lower levels of fasting insulin, homeostatic model assessment–insulin resistance, and glycosylated hemoglobin A1c were found in exercise groups. Compared with controls, exercise groups had higher levels of interleukin-18 and lower levels of leptin, fibrinogen, and angiotensin II. In addition, we found that the exercise effects were modified by age, sex, and health status such that people aged <50 years, men, and people with type 2 diabetes, hypertension, dyslipidemia, or metabolic syndrome appeared to benefit more.

Conclusions—This meta-analysis showed that exercise significantly improved cardiorespiratory fitness and some cardiometabolic biomarkers. The effects of exercise were modified by age, sex, and health status. Findings from this study have significant implications for future design of targeted lifestyle interventions. **(*J Am Heart Assoc*. 2015;4:e002014 doi: 10.1161/JAHA.115.002014)**

Key Words: biomarker • cardiometabolic health • cardiovascular disease prevention • exercise training

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality affecting ≈84 million people in the United States.[1–3] Current guidelines recommend exercise for both primary and secondary prevention of CVD.[4–6] Observational studies have associated exercise with lower CVD risk in populations free of preexisting CVD.[7–9] Substantial evidence from secondary prevention studies also confirms better survival and reduced CVD recurrence after exercise interventions.[10,11] Because of apparent ethical and feasibility issues, however, no long-term randomized controlled trials (RCTs) have directly investigated the benefits and risks of exercise training in relation to CVD incidence.[12] Consequently, exercise

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interventions among healthy populations have focused on intermediate CVD biomarkers. Changes in circulating CVD biomarkers and cardiorespiratory fitness (CRF) are reasonable indicators for the favorable effects of exercise training on cardiovascular health.

An important component of health-related fitness, CRF refers to the capacity of respiratory and cardiovascular systems to provide muscles with oxygen during sustained and/or intense exercise. Available evidence has shown that CRF can significantly improve the predictive ability of both short- and long-term CVD risk when added to traditional risk factors.[13] In addition to serving as a diagnostic and prognostic health indicator in clinical settings, CRF has been used as an indicator of habitual exercise.[14,15]

Traditional CVD biomarkers, such as non–high-density lipoprotein cholesterol and high-sensitivity C-reactive protein, may also have the potential to be used in CVD risk prediction.[16–19] Although most previous studies examining the relationship between exercise and circulating biomarkers focus on commonly measured CVD biomarkers, an increasing number of studies are evaluating novel biomarkers.[20,21] Evidence has implicated, for example, relevant biomarkers in insulin resistance and inflammation that contribute to CVD development.[22–26]

Nevertheless, much remains uncertain concerning the effects of exercise on both traditional and novel CVD biomarkers for targeted interventions and clinical evaluations.[20,21,27] The primary objective of this meta-analysis was to assess the effects of exercise training on CRF and a variety of both traditional and novel circulating CVD biomarkers. Furthermore, we aimed to investigate the sources of heterogeneity, especially by potential effect modifiers such as age, sex, obesity, lifestyle, preexisting conditions (type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndrome), and intervention duration and intensity.

Methods

Data Sources and Searches

We developed and followed a standardized protocol to do this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28] Two investigators (X.L., X.Z.) independently conducted literature searches of Medline, Embase, and the Cochrane Central Register of Controlled Trials published from January 1965 (index date) to March 2014, using keywords and Medical Subject Headings (Table 1). All relevant studies and review articles (including meta-analysis) and the reference lists of the identified articles were checked manually. Any disagreements between 2 investigators were resolved by consensus. Institutional review board approval is not applicable because the current study is a systematic review and meta-analysis, which is not considered research involving human subjects.

Table 1. Search Strategy for Medline

1.	exp Exercise/
2.	physical activity.ab.
3.	aerobic*.ab.
4.	or/1 to 3
5.	exp Biological Markers/
6.	Exercise Tolerance/
7.	Exercise Test/
8.	exp Oxygen Consumption/
9.	Physical Fitness/
10.	or/5 to 9
11.	randomized controlled trial.pt.
12.	controlled clinical trial.pt.
13.	Randomized Controlled Trials/
14.	Random Allocation/
15.	Intervention Studies/
16.	or/11 to 15
17.	4 and 10
18.	17 and 16
19.	limit 18 to English language
20.	limit 19 to humans

Study Selection

Articles were included (1) if the study was an RCT that assigned at least 1 group of participants to exercise training and 1 group to control and (2) if CRF (absolute and relative maximal oxygen uptake) or circulating CVD biomarkers of lipid and lipoprotein metabolism, glucose intolerance and insulin resistance, systemic inflammation, or hemostasis were measured at baseline and at the end of the trial.

All abstracts about RCTs reporting the effect of exercise training on CVD-related biomarkers or CRF were included for screening. We excluded studies (1) if the study design was not a RCT; (2) if the exercise intervention was acute (≤1 week), because we are interested in the effects of exercise interventions of moderate to long duration; (3) if interventions were based on education or counseling rather than a structured exercise training assignment; (4) if maximal oxygen consumption, or VO_{2max}, was indirectly calculated through heart rate or fixed time testing and no other biomarkers of interest to this study were reported; (5) if levels of circulating biomarkers were not directly measured; (6) if values of outcome measures at the end of trials were not reported; (7) if participants had severe chronic diseases (preexisting CVD, liver or kidney diseases, or cancers), any other conditions that could potentially compromise participants' capacity to exercise (disability, frailty, declined activities of daily living, or wheelchair dependency), or any mental conditions (depression, anxiety, schizophrenia, bipolar disorder, Parkinson's disease, or Alzheimer's disease); (8) if participants were identified as trained professionals, athletes, or soldiers; (9) if participants were infants, children, or adolescents; or (10) if participants were pregnant, postpartum, nursing, had recent surgery, or were undergoing rehabilitation exercise. If multiple articles were published based on the same trial, data were retrieved as 1 independent trial. If there were duplicate results from the same trial, the most updated and comprehensive ones were extracted.

Data Extraction and Quality Assessment

In total, 6135 articles were retrieved from the literature search. We excluded 5796 articles after abstract review and 170 after full-text examination. Data extraction was conducted independently by 2 investigators (X.L., X.Z.), and discrepancies were resolved through consensus. The following information was extracted from all eligible studies: general information (first author's name, article title, and country of origin), study characteristics (study design, eligibility criteria, randomization, blinding, cointervention, dropout rate, and reason for dropping out), participant characteristics (age, sex, ethnicity, body mass index, life style, health status, and number of participants in each group), intervention and setting (exercise type, duration, intensity, and supervision), and outcome measures (definition of outcomes, statistical techniques, pre- and postintervention means, standard deviation, sample size of each arm, and adverse events). Maximal oxygen uptake VO_{2max} was measured directly and determined based on the highest VO_2 obtained prior to volitional fatigue. In this meta-analysis, we focused on biomarkers in blood samples, including plasma, serum, and whole blood. All samples for fasting glucose and insulin measurement in the studies were collected after >10 hours of fasting.

Data Synthesis and Analysis

Methodological quality was assessed by 2 investigators (X.L., X.Z.) using the Cochrane Collaboration's tool for assessing risk of bias.[29] This included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. For each trial, the risk of bias was reported as *low risk, unclear risk*, or *high risk*. Disagreement was resolved by discussion. All eligible comparisons from each trial were extracted separately according to exercise intensity. The criteria for classifying

Table 2. Criteria Used for Exercise Intensity Classification

	Moderate	Vigorous
Maximum heart rate, beats/min	<140	≥140
Maximum heart rate, %	<75	≥75
Speed of running, m/s	<6.8	≥6.8
Metabolic equivalents	Women: <6	Women: ≥6
	Men: <8	Men: ≥8
Oxygen uptake (% of VO_{2max})	<70	≥70
Relative metabolic rate	<8	≥8

exercise interventions as *moderate exercise* or *vigorous exercise* are summarized in Table 2. If the intensity measures were not reported in individual studies, maximum heart rate, maximum heart rate percentage, speed of running, metabolic equivalent, oxygen uptake, or relative metabolic rate were used to classify exercise intensity. To maintain independence, the most vigorous intervention and the control group in each trial were included in the primary analysis if multiple training groups of different intensities were compared with a single control group. Sensitivity analyses were performed by conducting separate analyses of all eligible comparisons for moderate and vigorous exercise interventions, respectively.

Mean levels and standard deviations of CRF and CVD biomarkers after the exercise interventions from individual trials were used to calculate weighted mean differences (WMDs) and 95% CIs using DerSimonian and Laird random-effects models.[30] Between-study heterogeneity was examined using Q statistics and I^2 statistics.[31,32] $I^2 \approx 25\%$, 50%, and 75% is suggestive, respectively, of low, medium, and high heterogeneity. Egger's tests were used to formally test publication bias.[33] If there was any evidence of publication bias, the trim and fill method was used to evaluate the impact of publication bias.[34]

All eligible trials were analyzed in subgroup analyses conducted within the strata of the predetermined potential modifiers, including age (mean or median <50 versus ≥50 years), sex (women versus men), body mass index (obese versus nonobese), lifestyle (active versus sedentary), health status (having at least 1 of the following comorbidities: type 2 diabetes, hypertension, hyperlipidemia, and metabolic syndrome versus none), and trial duration (≥16 versus <16 weeks). Obesity was defined as body mass index ≥30 kg/m^2. Active lifestyle was defined according to the report of individual trials. Health status was confirmed by clinical diagnosis or reported medication use. Metaregressions were performed to evaluate the overall impact of potential modifiers.

Two-sided $P \leq 0.05$ was used as the significance level except for the Q statistic and the Egger's tests (P=0.10).[35] All statistical analyses were performed with Stata statistical software version 12 (Stata Corp).

Results

Figure 1 shows the number of trials included in the analysis for each outcome. A total of 7487 participants aged between 18 and 90 years, from 169 articles based on 160 RCTs, were included in the meta-analysis. Characteristics of eligible studies are summarized in Table 3. Among all participants, 4276 (57.1%) were women; 3211 (42.9%) were men; 5845 (78.1%) were free of type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndrome; and 1640 (21.9%) had at least 1 of those conditions. The median duration of trials was 12 weeks (range: 2 weeks to 2 years).

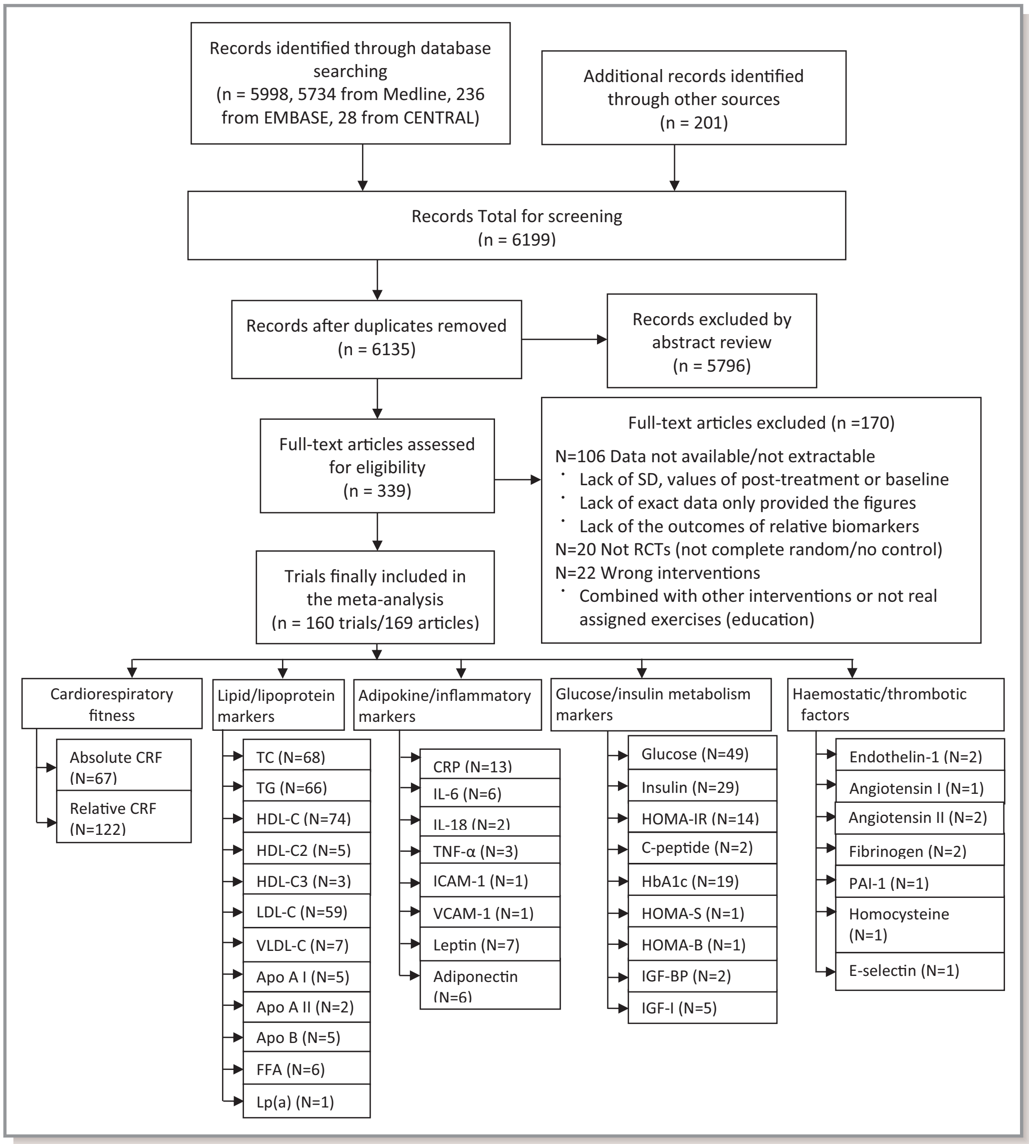

Figure 1. Summary of study selection process. In total, 6135 articles were retrieved from the literature search that evaluated the effect of exercise interventions on CRF or cardiometabolic biomarkers. We excluded 5796 articles after abstract review and 170 after full text examination. After exclusion, 160 RCTs reported in 169 articles were included in the meta-analysis. Apo AI indicates apolipoprotein A1; Apo AII, apolipoprotein A2; Apo B, apolipoprotein B; CRF, cardiorespiratory fitness; CRP, C-reactive protein; FFA, free fatty acid; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOME-B, homeostatic model assessment-beta cell function; HOMA-IR, homeostatic model assessment–insulin resistance; HOMA-S, homeostatic model assessment-insulin sensitivity; ICAM-1, intercellular adhesion molecule 1; IGF-1, insulin-like growth factor 1; IGF-BP, insulin-like growth factor binding protein; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PAI-1, plasminogen activator inhibitor-1; RCTs, randomized controlled trials; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; VLDL-C, very low-density lipoprotein cholesterol.

Table 3. Characteristics of the Trials Included in the Meta-Analysis

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Abderrahman, 2013[36]	Mean: 20.6	Male only	Mean: 22.8	7	NR/Health	Running/Vigorous/No	9/6	Absolute CRF, Relative CRF
Ahmaidi, 1998[37]	53 to 74	NR	NR	12	Sedentary/Health	Walking/Jogging/Vigorous/No	11/11	Absolute CRF, Relative CRF
Aldred, 1995[38]	41 to 55	Female only	T: 24.8±1.0 C: 26.8±0.8	12	Sedentary/Health	Walking/Moderate/No	11/11	TC, HDL-C2 LDL-C, FFA
Ashutosh, 1997[39]	20 to 60	Female only	Overweight or obesity	46	NR/Health	Aerobic exercise/NR/Dietary intervention	9/6	Absolute CRF, Relative CRF
Asikainen, 2002[40]	48 to 63	Female only	Mean: 26.2	24	Sedentary/Health	Walking/Vigorous/No	20/38	Relative CRF
Baker, 1986[41]	Mean: 58.2	Male only	NR	20	Sedentary/Health	Aerobic training/Vigorous/No	20/14	Absolute CRF, Relative CRF, TC, HDL-C, LDL-C, VLDL-C
Balducci, 2010, 2012[42]	C: 58.8±8.6 T: 58.8±8.5	NR	C: 31.9±4.6 T: 31.2±4.6	52	Sedentary/Diabetes mellitus	Aerobic and resistance training/Moderate/No	288/275	Relative CRF, TC, TG, HDL-C, LDL-C, CRP, Fasting glucose, Insulin, HOMA-IR HbA1c
Beavers, 2010[43]	60 to 79	Female: 67%	>28.0	78	Active/Health	Walking and interactive, health education in control	97/93	Leptin
Bell, 2010[44]	Male: 49±11 Female: 50±9	NR	Mean: 30	24	Sedentary/Health	Walking/Moderate/No	43/45	Absolute CRF, Relative CRF, TC, TG, HDL-C, LDL-C, Fasting glucose
Bermon, 1999[45]	67 to 80	Male: 16	T: 24.9±0.5 C: 25.9±0.6	8	Sedentary/Health	Strength training/Vigorous/No	16/16	IGF-1, IGF-BP
Biddle, 2011[46]	Mean: 34.8±12.6	Female 13	Mean: 36.3±6.7	4	Sedentary/Health	Small-sided games-based exercise/NR/No	9/7	Absolute CRF, Relative CRF, TC, TG, HDL-C, LDL-C, CRP, Fasting glucose, HbA1c
Blumenthal, 1991[47]	60 to 83	Female: 50%	NR	60	Sedentary/Health	Aerobic exercise or yoga/Vigorous/No	15/15	Absolute CRF, Relative CRF
Blumenthal, 1991[48]	29 to 59	Male: 62%	Mean: 26.9	16	NR/untreated mild hypertension	Aerobic exercise training/Joging	39/22	Absolute CRF, Relative CRF
Boardley, 2007[49]	≥65	Male: 27%	NR	16	Sedentary/Health	Resistance training and aerobic walking/Moderate/No	33/35	TC, TG, HDL-C, LDL-C
Bobeuf, 2011[50]	59 to 73	Female: 52.6%	Mean: 26.2±2.6	24	Sedentary/Health	Resistance training/Vigorous/Vitamins C/E supplementation	17/12	TC, TG, HDL-C, LDL-C
Boreham, 2000[51]	18 to 22	Female only	NR	7	Sedentary/Health	Stair climbing/Moderate/No	12/10	TC, HDL-C

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Boudou, 2003[52]	Mean: 45.4±7.2	Male only	Mean: 29.6±4.6	8	NR/Diabetes mellitus	Endurance exercise/ Vigorous/No	8/8	Adiponectin, Leptin, Insulin
Bourque, 1997[53]	23 to 43	Female only	Mean: 23.1±4.9	12	Sedentary/Health	Endurance exercise/ Vigorous/No	6/7	Relative CRF
Braith, 1994[54]	60 to 79	Female: 54.5%	NR	24	Sedentary/Health	Walking/Vigorous/No	14/11	Relative CRF
Broeder, 1992[55]	18 to 35	Male only	Mean: 25.3	12	NR/Health	Walk or jog/Vigorous/No	15/19	Relative CRF
Broman, 2006[56]	69±4	Female only	NR	8	NR/Health	In deep water running/ Walking/Vigorous/No	15/9	Absolute CRF, Relative CRF
Burr, 2011[57]	Mean: 26	NR	NR	6	Sedentary/Health	Vehicle riding/Vigorous/No	34/12	Relative CRF, Fasting glucose
Camargo, 2008[58]	Mean: 29	Male only	Mean: 27.3	12	Sedentary/Health	Aerobic training/Moderate/ No	7/7	Relative CRF
Campbell, 2007[59]	40 to 75	Female only	29.9 to 28.7	52	Sedentary/Health	Aerobic Exercise/Moderate/ No	17/15	Absolute CRF, Relative CRF, CRP
Canuto, 2012[60]	18 to 64	Female only	Mean: 34.8	12	NR/Health	Resistance training/ Moderate/Education	29/30	TC, TG, HDL-C, LDL-C, CRP, Fasting glucose, Insulin, HbA1c
Carroll, 2012[61]	T: 39.3±7.8 C: 41.0±7.7	Female only	T: 39.9±7.4 C: 41.0±7.7	12	Sedentary/Health	Treadmill walking/Moderate/ Lifestyle intervention	22/22	Absolute CRF, Relative CRF
Chan, 2013[62]	Mean: 54±11	Female only	Mean: 31±7	10	Sedentary/ Hypertension	Treadmill walking/ Vigorous/Education	10/13	Relative CRF,
Chandler, 1996[63]	60 to 79	Female: 38.6%	NR	24	NR/Health	Endurance training/ Moderate/No	16/11	Relative CRF, PAI-1
Cho, 2011[64]	34 to 60	Female only	Mean: 25.6	12	Sedentary/Health	Walking/Moderate/No	13/10	Relative CRF,TG, HDL-C FFA, Fasting glucose, Insulin, HOMA-IR
Christiansen, 2010[65]	18 to 45	Female: 38	30 to 40	12	Sedentary/Health	Aerobic exercise/Vigorous/ Dietary intervention	21/19	Absolute CRF,TC, TG, HDL-C, FFA, IL-6, IL-18, Adiponectin, Fasting glucose, Insulin, HOMA-IR
Church, 2007[66]	45 to 75	Female only	25 to 43	24	Sedentary/Health	Aerobic exercise/Moderate/ No	103/102	Absolute CRF, relative CRF, TG, HDL-C, LDL-C, Fasting glucose
Ciolac, 2011[67]	20 to 30	Female only	Mean: 23.78	16	Sedentary/Health	Endurance exercise/ Vigorous/No	11/12	Relative CRF,TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin, HOMA-IR
Coker, 2009[68]	65 to 90	Female: 50%	26 to 37	12	NR/Health	Cycle ergometer/Moderate/ No	6/6	Absolute CRF

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Cortez-Cooper, 2008[69]	40 to 80	Female: 73.8%	<30	13	Sedentary/Health	Aerobic exercise strength training vs stretching/ Moderate/No	12/12	Relative CRF,TC, TG, HDL-C, LDL-C, Endothelin-1, Fasting glucose
Cox, 1993[70]	20 to 45	Male only	Mean: 26.3 (25.7 to 26.9)	4	Sedentary/Health	Not report/Vigorous/Drink low-alcohol beer or continue their normal drinking habits	19/16	TC, TG, HDL-C, HDL-C2, HDL-C3, LDL-C, Apo AI, Apo AII, Apo B
Cox, 2003[71]	Mean: 42.4±5.0	Male only	Overweight or obesity	16	Sedentary/ Hypertension	NR/Moderate & vigorous/ Dietary intervention and usual dietary	13/17	Absolute CRF
Dalleck, 2009[72]	45 to 75 year	Female only	Normal	12	Sedentary/Health	NR/Moderate/No	8/10	Absolute CRF, Relative CRF,TC, TG, HDL-C, LDL-C, Fasting glucose
De Vito, 1999[73]	60 to 70	Female only	NR	12	Sedentary/Health	Walking/Moderate/No	11/9	Absolute CRF, Relative CRF
Dimeo, 2012[74]	42 to 78	Female: 58%	Mean: 29.4	12	NR/Hyperlipidemia	Walking on a treadmill/NR/ No	22/25	Relative CRF
Dipietro, 2006[75]	62 to 84	Female only	Mean: 27.3	36	Sedentary/Health	Aerobic training/Moderate/ No	9/7	Relative CRF,FFA, Fasting glucose, Insulin
Duncan, 1991[76]	20 to 40	Female only	NR	24	Sedentary/Health	Walk/Moderate/No	12/13	Relative CRF,TC, TG, HDL-C, LDL-C
Duscha, 2005[77]	40 to 65	NR	25 to 35	36	NR/Hyperlipidemia	Walking/Moderate/No	25/37	Absolute CRF, Relative CRF
Eguchi, 2012[78]	20 to 65	Female only	Mean: 25.1±3.9	12	NR/Health	Endurance training using bicycle ergometers/ Moderate/No	8/10	Absolute CRF, Relative CRF,TC, TG, HDL-C, LDL-C, Fasting glucose, HbA1c
Fatouros, 2005[79]	65 to 78	Male only	28.7 to 30.2	24	Sedentary/Health	Resistance exercises/ Moderate/No	12/10	Relative CRF, Adiponectin, Leptin, Fasting glucose, HOMA-IR
Finucane, 2010[80]	67.4 to 76.3	Female: 44%	Mean: 27.2	12	NR/Health	Cycle ergometer/Moderate/ No	48/48	TC, TG, HDL-C, LDL-C, Fasting glucose, HbA1c
Friedenreich, 2011[81]	50 to 74	Female only	22 to 40	52	Sedentary/Health	Aerobic exercise/Vigorous/ No	154/154	Adiponectin, Leptin, Fasting glucose, Insulin, HOMA-IR, IGF-1, IGF-BP
Garber, 1992[82]	24 to 50	Female: 75%	NR	8	Sedentary/Health	Walk-jog/Moderate/No	13/9	Relative CRF
Geogiades, 2000[83]	≥29	Female: 44%	25 to 37	24	Sedentary/ Hypertension	Aerobic exercise/Vigorous/ No	36/19	Relative CRF
Gormley, 2008[84]	18 to 31	Female: 65.5%	Mean: 24.3	6	Sedentary/Health	Aerobic/Moderate/No	14/13	Relative CRF

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m²	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Gram, 2010[85]	25 to 80	Female: 45.6%	NR	52	NR/Diabetes mellitus	Strength training and aerobic exercise/Moderate/No	21/20	Absolute CRF,TC, HDL-C, LDL-C, HbA1c
Grandjean, 1996[86]	NR	Female only	NR	24	Sedentary/Health	Walking and jog and cycling/Vigorous/No	20/17	Absolute CRF,TC, TG, HDL-C, LDL-C, VLDL-C
Gray, 2009[87]	18 to 65	Female: 77%	Mean: 28.6	12	Sedentary/Health	Pedometer-based walking/Moderate/No	24/24	CRP, IL-6, TNF-α, Fasting glucose, Insulin, HOMA-IR
Guadalupe-Grau, 2009[88]	Mean: 23.9±2.4	Female: 34.8%	C: 24.0±3.6 T: 22.8±2.0	9	Active/Health	Strength combined with plyometric jumps training/Vigorous/No	8/15	Leptin
Hagan, 1986[89]	Mean: 36.6	Female: 50%	Normal	12	Sedentary/Health	Aerobic training/Moderate/Dietary training	12/12	Absolute CRF, Relative CRF, TC, TG, HDL-C, LDL-C, VLDL-C
Hass, 2001[90]	35 to 55	Female: 50%	NR	12	Sedentary/Health	NR/Moderate/No	17/9	Absolute CRF, Relative CRF
Hendrickson, 2010[91]	18 to 26	Female only	NR	12	Active/Health	Aerobic endurance and strength training/Vigorous/No	13/10	Relative CRF
Heydari, 2013[92]	Mean: 24.9±4.3	Male only	Mean: 28.7±3.1	12	Sedentary/Health	High-intensity intermittent exercise/Vigorous/No	20/18	Absolute CRF, Relative CRF
Heydari, 2013[92]	Mean: 24.9±4.3	Male only	Mean: 28.7	12	Active/Health	High-intensity intermittent exercise/Vigorous/No	25/21	Absolute CRF, Relative CRF
Hilberg, 2013[93]	T: 49±6 C: 48±6	Male only	NR	12	NR/Health	NR/Vigorous/No	22/22	Relative CRF
Hiruntrakul, 2010[94]	18 to 25	Male only	C: 21.35±3.54 T: 20.99±3.35	12	Sedentary/Health	Aerobic exercise/Moderate/No	19/18	Relative CRF, HDL-C
Ho, 2012[95]	40 to 66	Female: 83.5%	25 to 40	12	Sedentary/Health	Aerobic resistance training/Moderate/No	15/16	Relative CRF, TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin
Hu, 2009[96]	20 to 45	Male only	NR	10	Sedentary/Health	Progressive strength training/Moderate/No	48/21	Absolute CRF, Relative CRF,
Huttunen, 1979[97]	40 to 45	Male only	NR	16	Sedentary/Health	Walking, Jogging, Swimming, Skiing, or Cycling/Moderate/No	44/46	Relative CRF, HDL-C, Apo AI, Apo AII
Tsuji, 2000[98]	60 to 81	Female: 53%	NR	25	Active/Health	Endurance session with a bicycle ergometer, and a resistance exercise training session using rubber films/Moderate/Education	31/33	Relative CRF

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Irwin, 2012[99]	59 to 86	Female: 61%	NR	9	Sedentary/Health	Tai Chi Chih vs health education/Moderate/No	46/37	CRP, IL-6, IL-18
Larose, 2011[100]	39 to 70	Female 36.2%	Mean: 34.9	24	Sedentary/Diabetes mellitus	Aerobic or resistance training/Vigorous/No	60/63	Relative CRF, HbA1c
Jessup, 1998[101]	61 to 77	Female: 52%	NR	16	Sedentary/Health	Treadmills and stair-climbers/Vigorous/No	11/10	Relative CRF
Kadoglou, 2012[102]	Mean: 61.3±2.1	Female: 67.6%	T: 32.74±4.05 C: 31.58±5.71	12	NR/Diabetes mellitus	Resistance Exercise/Vigorous/No	23/24	Relative CRF, TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin, HOMA-IR, HbA1c, Fibrinogen
Karstoft, 2013[103]	C: 57.1±3.0 T: 60.8±2.2	Female: 31%	NR	16	NR/Diabetes mellitus	Walking/Moderate/No	12/8	Absolute CRF, Relative CRF, TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin, HbA1c
King, 1989[104]	Male 49±6 Female 47±5	Female: 50%	NR	24	Sedentary/Health	Aerobic/Exercise/Training/Moderate/No	29/28	Relative CRF
Kirk, 2003[105]	19 to 30	Male only	27 to 32	36	Sedentary/Health	Aerobic exercise/Moderate/No	16/15	Absolute CRF, Relative CRF
Kirk, 2003[105]	19 to 30	Female only	27 to 32	36	Sedentary/Health	Aerobic Exercise/Moderate/No	25/18	Absolute CRF, Relative CRF
Kiviniemi, 2007[106]	T: 31±6 C 35±8	Male only	T: 24±2 C: 25±1	4	Active/Health	Running/Vigorous/No	9/10	Absolute CRF, Relative CRF
Kokkinos, 1998[107]	35 to 76	Male only	T: 30±4 C: 31±5	16	Sedentary/Hypertension	Aerobic/Exercise/Moderate/No	15/19	TC, TG, HDL-C, HDL-C2, HDL-C3, LDL-C, Apo AI, Apo B
Kraemer, 1997,[108] 1999[109]	Mean: 35.4±8.5	Female only	C: 28.2±4.0 T: 28.3±4.2	12	NR/Health	Aerobic endurance exercise/Vigorous/Dietary intervention	9/8	Absolute CRF, Relative CRF, TG, Fasting glucose
Krogh, 2012[110]	18 to 60	Female: 67%	NR	12	NR/Health	Aerobic exercise/Vigorous/No	56/59	Relative CRF, TC, TG, HDL-C, Fasting glucose, Insulin
Krustrup, 2009[111]	20 to 43	Male only	Mean: 25.7	12	Sedentary/Health	Recreational soccer/Vigorous/No	12/10	Relative CRF, TC, HDL-C, LDL-C,Absolute CRF, CRP, Fasting glucose, Insulin
Kukkonen-Harjula, 1998[112]	31 to 52	Female: 53%	18.5 to 32.7	15	Sedentary/Health	Walking/Training/Moderate/No	58/58	Absolute CRF, Relative CRF, Fibrinogen
Kurban, 2011[113]	T: 53.77±8.2 C: 53.57±6.6	Female: 51.7%	T: 30.90±4.64 C: 30.23±4.74	12	Sedentary/Diabetes Mellitus	Walking/Moderate/No	30/30	Fasting glucose, HbA1c

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Laaksonen, 2000[114]	20 to 40	Male only	Mean: 24.4	16	Active/Diabetes mellitus	Sustained running/ Moderate/No	20/22	Relative CRF, TC, TG, HDL-C, LDL-C, Apo AI, Apo B, HbA1c
Labrunee, 2012[115]	Mean: 52.7±8.2	Female: 82.6%	Mean: 38.5±7.6	12	NR/Diabetes mellitus	Cyclergometer training/NR/ No	11/12	Relative CRF, TC, TG, HDL-C, LDL-C, Fasting glucose, HOMA-IR, HbA1c
Lake, 1996[116]	18 to 28	Male only	NR	6	Active/Health	Running training/Moderate/ No	8/7	Relative CRF
LaPerriere, 1994[117]	18 to 40	Male only	NR	10	Sedentary/Health	Aerobic exercise/Vigorous/ No	7/7	Relative CRF
Lee, 2003[118]	18 to 30	Male only	NR	2	Sedentary/Health	Cycle ergometer/Vigorous/ No	12/12	Relative CRF
Lee, 2012[119]	30 to 50	Female only	≥25	14	NR/Health	NR/Moderate/No	8/7	Relative CRF, TC, TG, HDL-C, LDL-C, CRP, IL-6, TNF-α
LeMura, 2000[120]	Mean: 20.4±1	Female only	T: 20.8±2.1 C: 21.8±2.3	16	Sedentary/Health	Resistance training and aerobic training/ Vigorous/No	10/12	Relative CRF,TC, TG, HDL-C, LDL-C
Libardi, 2012[121]	T 48.6+5.0 C 49.1+5.5	Male only	T: 27.5+4.1 C: 24.7+3.3	24	Sedentary/Health	Resistance training/ Moderate/No	12/13	Relative CRF, TC, TG, HDL-C, LDL-C, CRP, IL-6, TNF-α, Fasting glucose
de Lima, 2012[122]	20 to 35	Female only	C: 23.0±2.4 T: 22.8±3.6	12	Sedentary/Health	Muscular endurance/ Moderate/No	10/8	Relative CRF
Lovell, 2011[123]	70 to 80	Male only	NR	20	Active/Health	Cycle ergometer and stretching/Vigorous/No	12/12	Absolute CRF, Relative CRF
Martin, 1990[124]	T: 58.6±4.6 C 60.6±7.4	Female only	NR	12	Sedentary/Health	Cycle ergometer training/ Vigorous/No	14/14	Absolute CRF, Relative CRF
McAuley, 2002[125]	25 to 70	Female: 67%	<27	16	NR/Health	NR/Moderate/Dietary intervention	29/23	TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin
Meckling, 2007[126]	20 to 62	Female only	25 to 30	12	NR/Health	Resistance training and endurance training/ Moderate and vigorous/ Dietary intervention or high protein	11/8	TC, TG, HDL-C, Fasting glucose, Insulin
Meyer, 2006[127]	30 to 60	Female: 47%	NR	12	Sedentary/Health	Walking or running/ Vigorous/No	12/13	Relative CRF
Miyaki, 2012[128]	Mean: 60±6	Female only	NR	8	Sedentary/Health	Walking and cycling/ Moderate/No	11/11	Relative CRF, TC, TG, HDL-C, LDL-C, Fasting glucose

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Morey, 2012[129]	60 to 89	Female: 3%	25 to 45 kg/m^2	52	NR/Health	Enhanced fitness intervention/NR/No	180/122	TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin, HOMA-IR HbA1c
Morgan, 2010[130]	50 to 70	Females: 73.3%	NR	15	Sedentary/Health	Walk/Moderate/No	14/15	TC, HDL-C
Morton, 2010[131]	T: 61+10 C: 63+9	Females: 22.2%	T: 32+7 C: 30.9+7.0	7	Sedentary/Diabetes mellitus	Walking/Vigorous/No	15/12	Absolute CRF, Relative CRF, Fasting glucose, HbA1c
Murphy, 2006[132]	Mean: 41.5±9.3	Female: 64.9%	T: 26.8±5.6 C: 24.4±3.6	8	Sedentary/Health	Walking/Moderate/No	21/12	TC, TG, HDL-C, LDL-C, CRP
Murtagh, 2005[133]	Mean: 45.7±9.4	Female: 64.6%	<30	12	Sedentary/Health	Walking/Vigorous/No	18/11	Relative CRF, TC, TG, HDL-C, LDL-C
Musa, 2009[134]	21 to 36	Male only	Normal	8	Sedentary/Health	Interval running/Moderate/No	20/16	TC, HDL-C
Nemoto, 2007[135]	Mean: 63±6	Female: 75.6%	C: 22.8 T moderate: 22.8 vigorous: 22.9	20	NR/Health	Walking/Moderate/No	43/37	Absolute CRF
Nicklas, 2009[136]	50 to 70	Female only	25 to 40	20	Sedentary/Health	Calorie restriction and aerobic exercise/ Moderate/dietary intervention	36/29	TG, HDL-C, LDL-C, Fasting glucose, Insulin
Niederseer, 2011[137]	T: 66.6±2.1 C: 67.3±4.4	Female: 47.6%	T: 27.1±3.3 C: 25.4±2.8	12	Active/Health	Skiing/Moderate/No	22/20	Relative CRF, TC, TG, HDL-C, LDL-C, CRP VCAM-1, ICAM-1, Endothelin-1, e_selectin
Nieman, 1993[138]	67 to 85	Female only	Mean: 23.7	12	Sedentary/Health	Walk/Moderate/No	14/16	Relative CRF, TC, TG, HDL-C, LDL-C,
Nieman, 1998[139]	Mean: 45.6±1.1	Female only	Mean: 33.1±0.6	12	Active/Health	Walking/Moderate and vigorous/dietary intervention	22/26	Absolute CRF, TC, Fasting glucose
Nordby, 2012[140]	20 to 40	Male only	25 to 30	12	Sedentary/Health	Endurance training (cycling, running, cross-training, or rowing)/Moderate/Dietary intervention	12/12	Absolute CRF, Relative CRF, Fasting glucose, Insulin, HbA1c
O'donovan, 2005[141]	30 to 45	Male only	NR	24	Sedentary/Health	NR/Moderate/No	14/15	Absolute CRF, Relative CRF, TC, TG, HDL-C, LDL-C, Fibrinogen
Panton, 1990[142] Pollock, 1991[143]	70 to 79	Female: 53.1%	NR	24	Sedentary/Health	Aerobic and resistance training/NR/No	13/15	Relative CRF

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Phillips, 2012[144]	62 to 67	Female only	Overweight or Obesity	12	Active/Health	Aerobic training/Vigorous/No	11/12	Leptin
Poehlman, 2000[145]	18 to 35	Female only	C: 22±2 T: 22±2	24	Sedentary/Health	Endurance training (N=14), resistance training/Vigorous/No	14/20	Absolute CRF
Posner, 1992[146]	60 to 86	Female: 61.9%	NR	16	Sedentary/Health	Cycle ergometer/Moderate/No	166/81	Absolute CRF, Relative CRF
Probart, 1991[147]	≥70	Female only	Mean: 24.6	26	NR/Health	Walking on a treadmill/Vigorous/No	10/6	Absolute CRF, Relative CRF
Pyka, 1994[148]	64 to 78	Female: 60%	NR	104	NR/Health	Resistance exercise (walking and stretching)/Moderate/No	8/6	IGF-1
Chow, 1987[149]	50 to 62	Female only	NR	52	NR/Health	Aerobic exercise or aerobic and strengthening exercises/Vigorous/No	17/15	Relative CRF
Raz, 1988[150]	24 to 26	Male only	Mean: 22.8	9	Sedentary/Health	Aerobic exercise/Vigorous/No	28/27	Relative CRF, TC, TG, HDL-C, HDL-C2, HDL-C3, LDL-C, HbA1c
Ready, 1996[151]	≥50	Female only	NR	24	Sedentary/Health	Walk/Moderate/No	17/18	Absolute CRF, Relative CRF, TC, TG, HDL-C, LDL-C
Romero-Arenas, 2013[152]	55 to 75	NR	Mean: 29.9	12	Active/Health	Resistance training/Moderate/No	16/10	Relative CRF
Santa-Clara, 2003,[153] 2006[154]	45 to 70	Female only	Caucasian-American T: 25±3 C: 27±5 African-American T: 29±7 C: 29±6	24	Sedentary/Health	Treadmill walking/Jogging, stationary cycling, and rowing/Vigorous/No	17/16	Relative CRF, IGF I
Santiago, 1995[155]	22 to 40	Female only	≥31	40	Sedentary/Hyperlipidemia	Walking/Vigorous/No	16/11	Relative CRF, TC, TG, HDL-C, LDL-C
Scanga, 1998[156]	Mean: 38±7	Female only	C: 35.2±3.9 T: 36.6±4.3	8	NR/Health	Aerobic and resistance training/Moderate/Dietary intervention	10/12	Absolute CRF, Relative CRF
Seifert, 2009[157]	C: 30±5 T: 32±6	Male only	25 to 30	12	Sedentary/Health	Endurance training/Moderate/Endurance training	10/7	Fasting glucose

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Lamina, 2011[158]	50 to 70	Male only	20 to 30	8	Sedentary/ Hypertension	Bicycle ergometer/ Vigorous/No	112/105	Relative CRF
Sillanpaa, 2009,[159] 2010[160]	39 to 64	Female only	Normal	21	NR/Health	NR/Vigorous/	15/12	TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin
Sloan, 2013[161]	T: 54.1±5.8 C: 54.1±4.9	Female only	T: 29.2±4.9 C: 27.1±5.9	16	Sedentary/Health	Walking/Moderate/No	16/16	Relative CRF
Spence, 2013[162]	NR	Male only	T: 73.0±16.9 C: 81.7±15.23	24	Active/Health	Endurance vs resistance/ Moderate/No	10/13	Absolute CRF, Relative CRF
Stachenfeld, 1998[163]	> 65	Female only	NR	24	Active/Health	Aerobic training/Vigorous/ No	9/8	Relative CRF
Stein, 1992[164]	T: 46.2±6.1 C: 45.0±6.1	Male only	NR	8	Sedentary/Health	Aerobic exercise training/ Moderate/No	19/14	Absolute CRF
Stensel, 1993[165]	42 to 59	Male only	Normal	52	Sedentary/Health	Brisk/Walking/Moderate/ No	24/24	TC, TG, HDL-C, LDL-C, VLDL-C, Apo AI, Apo B, Lp-A
Stensvold, 2010[166]	Mean: 50.2±9.5	Female: 39.5%	C: 31.9±4.1 T: 32.2±4.2	12	Sedentary/Health	Strength training vs aerobic interval training/Vigorous/ No	11/10	Relative CRF, TC, TG, HDL-C, Fasting glucose, C-peptide, HbA1c
Strasser, 2009[167]	>70	Females: 55.6%	Mean: 26.9	24	Sedentary/Health	Endurance training or–and resistance training/ Vigorous/No	13/14	Relative CRF
Sung, 2012[168]	>70	Female: 65%	NR	24	NR/Diabetes mellitus	Walking/Moderate/No	22/18	TC, TG, HDL-C, LDL-C, Fasting glucose, HbA1c
Takeshima, 2002[169]	60 to 75	Female only	NR	7	Sedentary/Health	Stretching, endurance-type exercise (walking and dancing, 30 min), Resistance exercise/ Vigorous/No	15/15	TC, TG, HDL-C, LDL-C
Takeshima, 2004[170]	60 to 83	8 Males and 10 Females	NR	12	Sedentary/Health	Progressive accommodating circuit exercise/Vigorous/ No	18/17	Absolute CRF, TC, TG, HDL-C, LDL-C
Thomas, 1984[171]	18 to 32	Female only	NR	12	Active/Health	Running/Vigorous/No	9/6	Absolute CRF, Relative CRF, TC, TG, HDL-C
Thompson, 2010[172]	45 to 64	Male only	C: 28.0±2.7 T: 28.5±2.9	24	Sedentary/Health	NR/Moderate/Dietary intervention	20/21	Relative CRF,TC, TG, HDL-C, CRP, IL-6, Fasting glucose, Insulin, HOMA-IR

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Tjonna, 2008[173]	Mean: 52.3±3.7	Female: 53.6%	C: 32.1±3.3 T: 29.4±4.9	16	NR/Health	Aerobic interval training/ Vigorous/No	8/9	Relative CRF, TG, HDL-C, Adiponectin, Fasting glucose, Insulin, HOMA-B
Toledo, 2008[174]	>30	Female: 62.5%	T: 34.8±1.1 C: 33.4±1.2	16	Sedentary/Health	Walking/Moderate/Dietary training	9/7	FFA, Fasting glucose, Insulin
Tseng, 2013[175]	18 to 29	Male only		12	NR/Health	Aerobic, resistance or combined aerobic and resistance training/ Moderate/	10/10	TG, HDL-C, Fasting glucose
Tulppo, 2003[176]	35±10	Male only	Moderate: 25±3 Vigorous: 25±2 C: 25±3	8	Sedentary/Health	Walking and Jogging/ Vigorous/No	16/11	Absolute CRF, Relative CRF
Utter, 1998[177]	25 to 75	Female only	25 to 65	12	Sedentary/Health	Walk/Moderate and vigorous/Dietary intervention	21/22	Absolute CRF, Relative CRF
Van Aggel-Leijssen, 2001,[178] 2001[179]	C: 38.6±6.5 T: 39.3±7.7	Male only	C: 32.6±2.5 T: 32.0±2.1	12	Sedentary/Health	Cycling on an ergometer, walking, and aqua-jogging/Moderate/Energy restriction and dietary intervention	20/17	Absolute CRF, FFA, Fasting glucose, Insulin
Van Den Berg, 2010[180]	18 to 30	Male only	NR	7	Sedentary/Health	Motor-driven treadmill/ Moderate/No	9/13	Absolute CRF, Relative CRF
Vicente-Campos, 2012[181]	62 to 67	Female: 60%	NR	28	Sedentary/Health	Aerobic training/Vigorous/ No	22/21	TC, TG, HDL-C, LDL-C
Vincent, 2002[182]	60 to 83	Female and Male	NR	24	Sedentary/Health	Resistance training/ Moderate/No	24/16	Relative CRF
Vissers, 2010[183]	C: 44.8±11.4 T: 44.7±13.0	Female: 74.7%	C: 29.8±2.6 T: 33.1±3.4	52	Active/Health	Bicycle ergometer/ Vigorous/No	20/20	TG, HDL-C
Vitiello, 1997[184]	Male: 66.9±1.0 Female: 67.1±1.7	Female: 40.3%	NR	24	Sedentary/Health	Endurance or stretching/ Flexibility/Moderate/No	30/22	Relative CRF, IGF-1
Volpe, 2008[185]	Mean: 44.2±7.2	Female only	Mean: 30.5±2.7	52	Sedentary/Health	Skiing/NR/Dietary intervention	14/14	TC, TG, HDL-C, LDL-C
Waib, 2011[186]	47 to 56	Training: 60.8%	T: 30.0 (28.8 to 31.2) C: 29.6 (27.8 to 31.5)	15	Sedentary/ Hypertension	Aerobic training jogging on an electronic treadmill/ Moderate/No	55/24	Relative CRF, HOMA-IR, C-peptide

Continued

Table 3. Continued

Study	Age, y	Sex	BMI, kg/m^2	Duration, wk	Activity/Medical Condition	Exercise Type, Intensity and Cointerventions	N_T/N_C	Marker
Wallman, 2009[187]	18 to 64	Female: 75%	Mean: 30±2	8	Sedentary/Health	Aerobic Exercise/Vigorous/ Dietary education	6/8	TC, TG, HDL-C, LDL-C
Wang, 2005[188]	C: 24.7±2.3 T: 23.5±1.6	Male only	C: 22.7±1.7 T: 23.1±0.6	8	Sedentary/Health	Bicycle ergometer/ Moderate/No	15/15	Relative CRF
Wang, 2011[189]	T: 21.5±0.7 C: 22.9±0.4	Male only	T: 22.9±0.4 C: 23.3±0.7	4	Sedentary/Health	Bicycle ergometer/ Moderate/No	10/10	Relative CRF
Warner, 1989[190]	27 to 63	Female: 35.3%	NR	12	Sedentary/ Hyperlipidemia	Aerobic training/Vigorous/ Fish oil intervention	7/7	Relative CRF, LDL-C, Apo B
Warren, 1993[191]	Mean: 73.6±0.7	Female only	Normal	12	Sedentary/Health	Walking or calisthenics control/Moderate/No	14/16	Relative CRF
Watkins, 2003[192]	NR	NR	T: 33.4±4.5 C: 34.0±5.2	24	Sedentary/Health	Aerobic training/Vigorous/ Weight lost	14/9	Relative CRF,TC, TG, HDL-C, LDL-C, Fasting glucose, Insulin
Wong, 1990[193]	Mean: 62.7±3.1	Male only	Normal	52	NR/Health	Treadmill walking/ Moderate/No	69/69	Absolute CRF,
Woods, 1999[194]	Mean: 65±0.8	NR	NR	24	Sedentary/Health	Aerobic exercise/ Moderate/No	14/15	Absolute CRF, Relative CRF
Wu, 2011[195]	45 to 64	Female: 71.9%	16.0 to 33.3	36	NR/Health	Aerobic exercise, stretching exercise/Vigorous/No	68/67	TG, Adiponectin, Fasting glucose, Insulin, HOMA-IR
Yoshizawa, 2009[196]	50 to 65	Female only	Mean: 23.7	8	Sedentary/Health	Resistance training/ Moderate/No	12/13	Relative CRF, TC, TG, HDL-C, LDL-C
Yoshizawa, 2009[197]	32 to 59	Female only	T: 24.6±1.1 C: 21.8±1.0	12	Sedentary/Health	Aerobic exercise training/ Moderate/No	12/12	Relative CRF, TC, HDL-C, LDL-C
You, 2006[198]	50 to 70	Female only	25 to 40	20	Sedentary/Health	Treadmill/Moderate/Dietary intervention	13/14	Absolute CRF, Relative CRF
Ziemann, 2011[199]	T: 21.6±1.1 C: 21.0±0.9	Male only	T: 24.5±1.8 C: 23.0±1.9	6	Active/Health	NR/Vigorous/Physical education	10/11	Absolute CRF, Relative CRF

Apo AI indicates apolipoprotein A1; Apo AII, apolipoprotein A2; Apo B, apolipoprotein B; BMI, body mass index; C, control group; CRF, cardiorespiratory fitness; CRP, C-reactive protein; FFA, free fatty acid; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; ICAM-1, intercellular adhesion molecule 1; IGF-1, insulin-like growth factor 1; IGF-BP, insulin-like growth factor binding protein; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; NR, not reported; PAI-1, plasminogen activator inhibitor-1; T, training group; TC, total cholesterol; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VLDL-C, very low-density lipoprotein cholesterol.

Description of Study Quality

The quality of studies included was heterogeneous (Figure 2). Random sequence generation was reported in 50 trials, and allocation concealment was reported in 20 trials; only 1 of these trials showed a high probability of selection bias because the random allocation was not concealed. The risk of potential performance bias was high in all trials because it was not possible to blind participants and trainers in exercise interventions. Among 26 trials reporting the blinding of outcome assessment, the risk of detection bias was high in only 1 trial. The risk of other bias was high in 46 trials because of poor compliance, the use of intention-to-treat analysis, limited sample sizes, or limitations discussed in individual articles.

Cardiorespiratory Fitness

A total of 67 and 123 independent comparisons were included in the primary analysis for absolute and relative CRF, respectively (Table 4). Both measures were significantly raised by exercise interventions (both $P<0.001$). The WMDs comparing exercise groups and control groups were 0.28 L/min (95% CI 0.23 to 0.33; $I^2=93.7\%$; $P<0.001$ for heterogeneity) for absolute CRF and 3.90 mL/kg per minute (95% CI 3.45 to 4.35; $I^2=91.4\%$; $P<0.001$ for heterogeneity) for relative CRF. The Egger's tests showed evidence of publication bias in both instances ($P<0.05$). When applying the trim and fill method, the conclusion regarding the associations between exercise training and CRF did not change (filled analysis for absolute CRF: WMD 0.14 L/min, 95% CI 0.20 to 5.28, $P<0.001$; filled analysis for relative CRF: WMD 2.56 mL/kg per minute, 95% CI 3.06 to 10.16, $P<0.001$).

Lipid and Lipoprotein Markers

The number of comparisons for each lipid and lipoprotein marker is shown in Table 4. Exercise training significantly lowered the levels of triglycerides ($P=0.02$) and increased the levels of high-density lipoprotein cholesterol (HDL-C; $P<0.001$) and apolipoprotein A1 ($P<0.001$). The WMDs were −5.31 mg/dL (95% CI −10.63 to −0.89; $I^2=71.8\%$; $P<0.001$ for heterogeneity) for triglycerides, 2.32 mg/dL (95% CI 1.16 to 3.87; $I^2=87.5\%$; $P<0.001$ for heterogeneity) for HDL-C, and 0.03 g/L (95% CI 0.02 to 0.04; $I^2=0.0\%$; $P=0.81$ for heterogeneity) for apolipoprotein A1. The *P* value of the Egger's test for HDL-C was 0.03, suggesting possible publication bias; however, the results from the trim and fill analysis did not show substantial impact of publication bias on the estimates or the statistics (filled analysis: WMD 2.32 mg/dL, 95% CI 1.16 to 3.87, $P<0.001$).

Adipokine and Inflammatory Markers

Significant associations were found for interleukin-18 (WMD 18.3 pg/mL; 95% CI 0.10 to 36.6; $I^2=0.0\%$; $P=0.95$ for heterogeneity) but not for C-reactive protein, interleukin-6, or tumor necrosis factor α in the primary analysis (Table 4). Although there was no effect on adiponectin, exercise training was significantly associated with reduced levels of leptin (WMD −2.72 ng/mL; 95% CI −4.03 to −1.42; $I^2=82.10\%$; $P<0.001$ for heterogeneity) (Table 4).

Markers of Glucose Intolerance and Insulin Resistance

Table 4 also shows the effects of exercise training on markers of glucose intolerance and insulin resistance. Fasting insulin

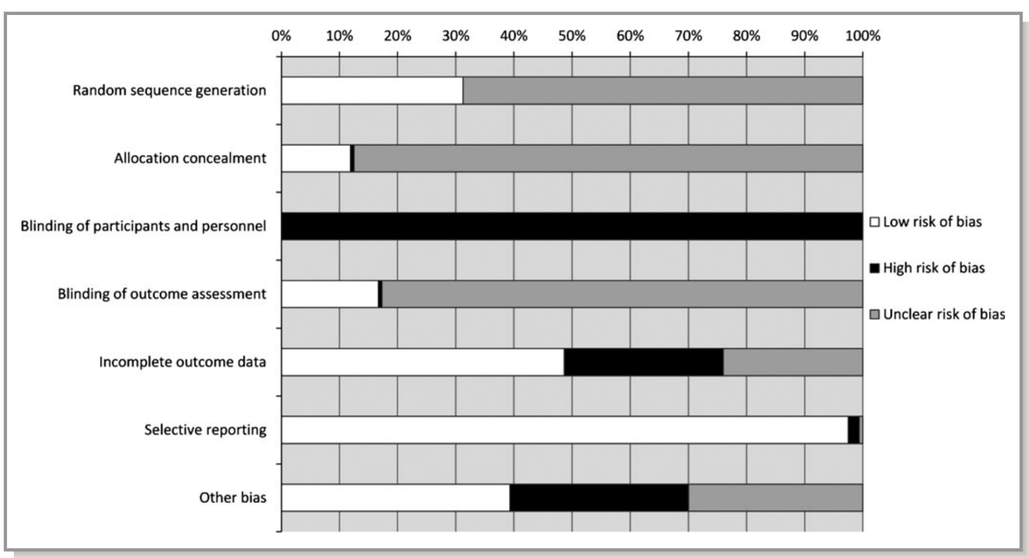

Figure 2. Assessment of risk of bias: summary for items of bias.

Table 4. WMDs in Cardiorespiratory Fitness and Circulating Concentrations of Biomarkers Between Exercise Groups and Control Groups

Outcome	No.*	Number of Participants		WMD	95% CI	P_{WMD}
		Exercise	Control			
Cardiorespiratory fitness						
Absolute, L/min	67	1448	1272	0.28	0.23 to 0.33	<0.001
Relative, mL/kg per minute	122	2543	2249	3.94	3.48 to 4.39	<0.001
Lipid and lipoprotein markers						
TC, mg/dL	68	1754	1604	1.16	−9.28 to 11.99	0.82
TG, mg/dL	66	1851	1703	−5.31	−10.63 to −0.89	0.02
HDL-C, mg/dL	74	1967	1800	2.32	1.16 to 3.87	<0.001
HDL_2-C, mg/dL	5	91	92	0.39	−1.93 to 2.32	0.8
HDL_3-C, mg/dL	3	62	62	−0.08	−1.55 to 1.55	0.94
LDL-C, mg/dL	59	1681	1525	3.87	−8.12 to 0.39	0.08
VLDL-C, mg/dL	7	130	102	−3.09	−8.51 to 2.32	0.29
Apo AI, g/L	5	63	62	0.03	0.02 to 0.04	<0.001
Apo AII, g/L	2	140	126	0.01	−0.01 to 0.03	0.2
Apo B, g/L	5	103	87	0.01	−0.01 to 0.03	0.4
FFA, mmol/L	6	70	62	−0.06	−0.14 to 0.03	0.21
Adipokine and inflammatory markers						
CRP, mg/L	13	598	554	−0.22	−0.78 to 0.34	0.44
IL-6, pg/mL	6	130	121	−0.05	−0.27 to 0.17	0.66
IL-18, pg/mL	2	67	56	18.3	0.10 to 36.6	0.05
TNF-α, pg/mL	3	43	44	0.21	−0.37 to 0.79	0.48
Adiponectin, μg/mL	6	273	267	0.52	−0.20 to 1.23	0.16
Leptin, ng/mL	7	312	315	−2.72	−4.03 to −1.42	<0.001
Glucose/insulin metabolism markers						
Glucose, mmol/L	49	1720	1569	−0.07	−0.13 to 0.004	0.06
Insulin, μIU/mL	29	1272	1149	−1.03	−1.69 to −0.37	0.002
HOMA-IR	14	1033	912	−0.3	−0.49 to −0.11	0.002
HbA1c, %	19	972	878	−0.28	−0.42 to −0.14	<0.001
C-peptide, nmol/L	2	66	34	−0.08	−0.29 to 0.46	0.67
IGF-1, ng/mL	5	230	207	3.16	−2.98 to 9.31	0.31
IGF-BP3, μg/mL	2	170	164	−0.002	−0.23 to 0.23	0.99
Hemostatic factors						
Fibrinogen, g/L	2	36	39	−0.39	−0.75 to −0.03	0.04
Endothelin-1, pg/mL	2	34	32	−0.22	−0.62 to 0.19	0.29
Angiotensin II, pg/mL	2	24	25	−1.32	−2.11 to −0.54	0.001

Apo AI indicates apolipoprotein A1; Apo AII, apolipoprotein A2; Apo B, apolipoprotein B; CRP, C-reactive protein; FFA, free fatty acid; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; IGF-1, insulin-like growth factor 1; IGF-BP3, insulin-like growth factor binding protein 3; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor α; VLDL-C, very low-density lipoprotein cholesterol; WMDs, weighted mean differences.
*Number of eligible independent comparisons.

levels; homeostatic model assessment–insulin resistance, or HOMA-IR; and glycosylated hemoglobin A1c were significantly lowered in exercise groups compared with control groups (P=0.002, P=0.002, and P<0.001) (Table 4). The WMDs between exercise groups and control groups were −1.03 μIU/mL (95% CI −1.69 to −0.37; I^2=79.8%; P<0.001

for heterogeneity) for fasting insulin. The WMD for HOMA-IR was −0.30 (95% CI −0.49 to −0.11; I^2=77.5%; *P*<0.001 for heterogeneity), whereas the WMD for hemoglobin A1c was −0.28% (95% CI −0.42 to −0.14; I^2=80.1%; *P*<0.001 for heterogeneity). The Egger's tests for fasting glucose and insulin were not suggestive of substantial publication bias (*P*=0.18 and *P*=0.24, respectively). The results from the trim and fill analysis suggested that there was no substantial impact of publication bias on the results for HOMA-IR or hemoglobin A1c (filled analysis for HOMA-IR: WMD −0.30, 95% CI −0.49 to −0.11, *P*=0.002; filled analysis for hemoglobin A1c: WMD −0.28%, 95% CI −0.42 to −0.14, *P*<0.001).

Hemostatic Factors

The primary analysis examined 3 hemostatic factors: fibrinogen, endothelin-1, and angiotensin II (Table 4). On average, the levels of fibrinogen and angiotensin II were 0.39 g/L (95% CI 0.03 to 0.75; I^2=45.00%; *P*=0.18 for heterogeneity) and 1.32 pg/mL (95% CI 0.54 to 2.11; I^2=0.00%; *P*=0.71 for heterogeneity) lower in exercise groups than in control groups. No significant association was found for endothelin-1.

Subgroup Analyses

Our metaregression results suggest that the differences in CRF between exercise and control groups were modified by age and sex (absolute CRF: *P*=0.008 and *P*<0.001 for age and sex, respectively; relative CRF: *P*=0.003 and *P*=0.001 for age and sex, respectively) (Table 5, Figure 3). In addition, the effects of exercise on levels of total cholesterol (*P*=0.04), low-density lipoprotein cholesterol (LDL-C; *P*=0.06), and fasting insulin (*P*=0.05) were modified by the presence of at least 1 of the following comorbidities: type 2 diabetes, hypertension, hyperlipidemia, and metabolic syndrome (Tables 6 and 7, Figure 3). Sex differences in the effects of exercise were also found for fasting insulin (*P*=0.04).

After conducting metaregressions, analyses within subgroups were performed. Compared with older people, those aged <50 years appeared to have larger changes in CRF. Consistent with the metaregression results, men seemed to have greater exercise-related improvement in CRF, LDL-C, and fasting insulin than women did (Figure 3). Exercise interventions appreciably improved the levels of total cholesterol, LDL-C, and fasting insulin (*P*=0.004, *P*=0.01, and *P*=0.01,

Table 5. WMDs in Absolute and Relative Cardiorespiratory Fitness Comparing Exercise Intervention Groups to Control Groups by Specific Modifiers

Modifier	Absolute CRF (L/min)					Relative CRF (mL/kg per minute)				
	n	WMD	95% CI	I^2, %	$P_{interaction}$*	n	WMD	95% CI	I^2, %	$P_{interaction}$
Age, y										
<50	16	0.47	0.34 to 0.60	93.4	0.008	28	5.60	4.56 to 6.65	85.1	0.003
≥50	12	0.21	0.11 to 0.32	84.0		30	3.31	2.46 to 4.15	91.0	
Sex										
Women	25	0.19	0.13 to 0.24	92.3	<0.001	48	3.24	2.61 to 3.87	88.7	0.001
Men	27	0.42	0.32 to 0.53	90.4		37	5.43	4.32 to 6.53	90.2	
Lifestyle										
Active	9	0.33	0.15 to 0.51	97.0	0.89	14	3.62	1.39 to 5.85	96.5	0.83
Sedentary	43	0.31	0.25 to 0.37	88.4		88	3.85	3.36 to 4.33	90.5	
BMI†										
Obese	19	0.28	0.20 to 0.36	93.3	0.65	19	3.85	2.83 to 4.87	94.9	0.96
Nonobese	20	0.26	0.17 to 0.36	89.1		46	4.01	3.22 to 4.79	85.7	
Health status‡										
Yes	8	0.33	0.07 to 0.60	88.2	0.84	16	3.34	2.63 to 4.04	74.8	0.46
None	53	0.27	0.22 to 0.33	94.6		94	4.10	3.51 to 4.71	92.7	
Duration, wk										
<16	39	0.33	0.25 to 0.40	91.3	0.09	69	3.83	3.12 to 4.54	90.7	0.72
≥16	28	0.21	0.15 to 0.28	92.3		54	3.90	3.34 to 4.35	90.4	

BMI indicates body mass index; CRF, cardiorespiratory fitness; WMDs, weighted mean differences,
**P* values for the impact of potential modifiers on the exercise effects.
†BMI in kg/m^2: obese ≥30; nonobese <30.
‡Health status: participants having at least 1 of type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndrome (yes) vs those with none of them (none).

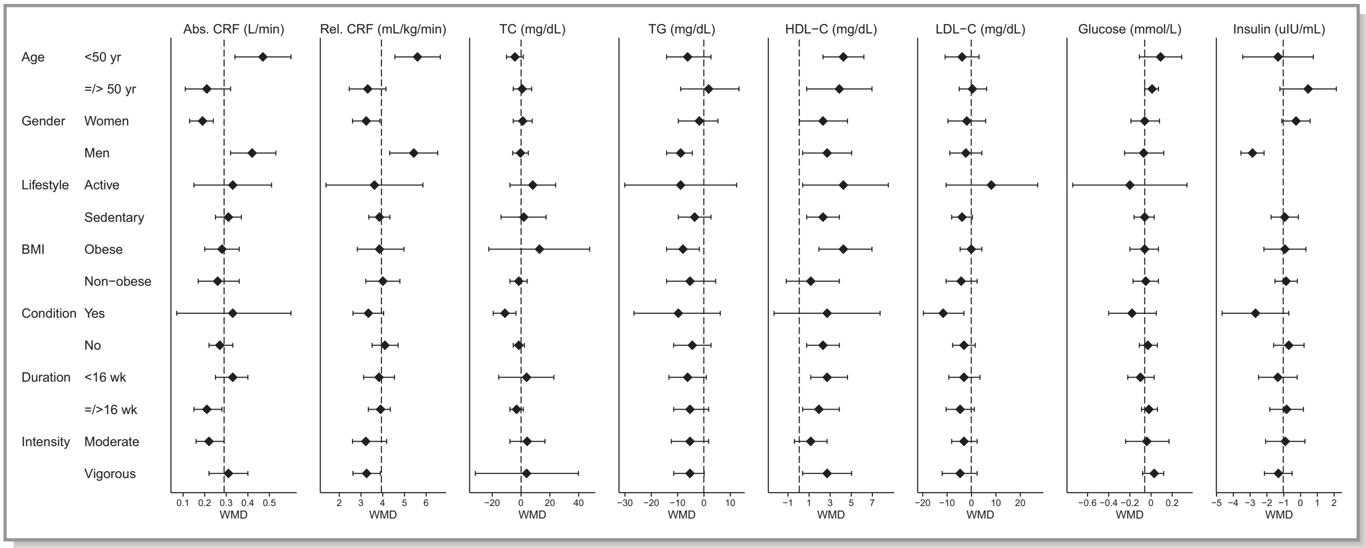

Figure 3. Forest plot of effects of exercise interventions on cardiorespiratory fitness, TC, TG, HDL-C, LDL-C, Fasting glucose, and fasting insulin within subgroups. The WMDs (diamonds) and corresponding CIs (extended line) between exercise groups and control groups are shown for each subgroup. Abs. CRF indicates absolute cardiorespiratory fitness; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Rel. CRF, relative cardiorespiratory fitness; TC, total cholesterol; TG, triglycerides; WMDs, weighted mean differences.

respectively) in people having at least 1 of type 2 diabetes, hypertension, hyperlipidemia, and metabolic syndrome (Tables 6 and 7, Figure 3); no such improvements were observed among people without any of those health conditions (P=0.44, P=0.19, and P=0.13, respectively) (Tables 6 and 7, Figure 3).

Sensitivity Analyses

In light of the potential impact of exercise intensity, we conducted separate analyses of all eligible comparisons for moderate and vigorous exercise interventions, respectively. The 95% CIs for moderate and vigorous interventions overlapped for both CRF measures and for all biomarkers (Table 8).

Discussion

This systematic review and meta-analysis of 160 RCTs involving 7487 participants indicates that exercise training may significantly improve CRF and CVD biomarkers of lipid and lipoprotein metabolism, glucose intolerance and insulin resistance, systemic inflammation, and hemostasis (Figure 4). In addition, we identified several important modifiers, including age, sex, and health status, that may partially modify the exercise effects on cardiovascular health.

The current meta-analysis shows that exercise, with relatively low risk of side effects compared with medications, may be an effective way to prevent CVD through impact on various biomarkers. Our results from the meta-analysis showed that exercise training significantly raised CRF, which has been demonstrated to be an independent predictor of CVD risk, CVD mortality, and total mortality.[200,201] Lower levels of triglycerides and higher levels of HDL-C were observed in exercise groups. Aside from conventional CVD biomarkers, our meta-analysis also examined the effects on biomarkers that have not been well studied in previous studies, including biomarkers of insulin resistance and hemostasis, adipokines, and novel lipid and inflammatory biomarkers. We found evidence supporting the favorable effects of exercise on apolipoprotein A1, interleukin-18, fasting insulin, HOMA-IR, and hemoglobin A1c. Although the exact biological mechanisms are not clear, our findings indicate that exercise may exert cardioprotective effects by altering dyslipidemia, inflammation, insulin resistance, and hemostasis.[19]

As a major component of HDL, apolipoprotein A1 plays an important role in the cardioprotective effects of HDL-C.[202–204] Our findings on apolipoprotein A1 strengthen the hypothesis that exercise may accelerate reverse cholesterol transport. Another plausible mechanism by which exercise improves the lipid profile is by regulation of lipoprotein lipase. Various studies have suggested that exercise may decrease the levels of triglycerides and increase the levels of HDL-C through its impact on lipoprotein lipase expression and activity, which were consistent with the results from our meta-analysis.[205–207] In addition, our analysis also confirmed that the proportion of CVD risk that could have been reduced by exercise via effects on total cholesterol and LDL-C is much lower than what has been observed previously.[208,209] Consequently, the results from our meta-analysis provide additional evidence in support

Table 6. WMDs in Lipid Biomarkers Comparing Exercise Intervention and Control Groups by Specific Modifiers

Modifier	Total Cholesterol (mg/dL)					Total Triglycerides (mg/dL)				
	n	WMD	95% CI	I^2, %	$P_{interaction}$*	n	WMD	95% CI	I^2, %	$P_{interaction}$
Age, y										
<50	12	−4.25	−10.1 to 1.55	0.0	0.43	12	−6.20	−14.2 to 2.66	34.3	0.21
≥50	15	0.77	−5.41 to 7.35	72.5		13	1.77	−8.86 to 13.3	75.5	
Sex										
Women	28	1.16	−5.41 to 7.73	91.6	0.61	27	−1.77	−9.74 to 5.31	76.1	0.25
Men	15	−0.39	−5.80 to 5.03	54.3		13	−8.86	−14.2 to −4.43	12.8	
Lifestyle										
Active	6	8.12	−7.73 to 24.0	92.5	0.71	5	−8.86	−30.1 to 12.4	61.2	0.64
Sedentary	47	1.93	−13.9 to 17.4	99.1		43	−3.54	−9.74 to 2.66	75.1	
BMI†										
Obese	16	12.8	−22.4 to 47.6	99.7	0.20	19	−7.97	−14.2 to −1.77	53.0	0.70
Nonobese	29	−1.55	−7.73 to 4.25	83.6		28	−5.31	−14.2 to 4.43	80.7	
Health status‡										
Yes	10	−11.2	−19.3 to −3.48	75.2	0.04	9	−9.74	−26.6 to 6.20	63.9	0.48
None	47	−1.55	−5.41 to 2.32	81.6		44	−4.43	−11.5 to 2.66	75.2	
Duration, wk										
<16	39	3.87	−15.5 to 22.8	82.9	0.34	35	−6.20	−13.3 to 0.89	71.1	0.76
≥16	29	−3.09	−7.73 to 1.55	99.2		31	−5.31	−11.5 to 1.77	72.7	
Modifier	**HDL-C (mg/dL)**					**LDL-C (mg/dL)**				
	N	WMD	95% CI	I^2, %	$P_{interaction}$*	N	WMD	95% CI	I^2, %	$P_{interaction}$
Age, y										
<50	16	4.25	2.32 to 6.19	73.9	0.94	9	−3.87	−10.8 to 3.09	49.3	0.38
≥50	15	3.87	0.77 to 6.96	84.5		14	0.39	−5.03 to 6.19	73.0	
Sex										
Women	28	2.32	0.08 to 4.64	84.8	0.80	24	−1.93	−9.67 to 5.80	95.0	0.93
Men	19	2.71	0.39 to 5.03	92.5		13	−2.32	−8.89 to 4.25	79.7	
Lifestyle										
Active	5	4.25	0.39 to 8.51	86.9	0.52	2	8.12	−10.4 to 27.1	54.9	0.21
Sedentary	52	2.32	0.77 to 3.87	18.6		45	−3.87	−8.12 to 0.39	88.3	
BMI†										
Obese	19	4.25	1.93 to 6.96	88.1	0.13	14	−0.08	−4.64 to 4.25	62.0	0.33
Nonobese	30	1.16	−1.16 to 3.87	83.0		25	−4.25	−10.4 to 2.32	91.4	
Health status‡										
Yes	11	2.71	−2.32 to 7.73	91.2	0.89	12	−11.6	−19.7 to −3.09	80.8	0.06
None	50	2.32	0.77 to 3.87	87.3		39	−3.09	−7.73 to 1.55	89.3	
Duration, wk										
<16	39	2.71	1.16 to 4.64	83.0	0.55	29	−3.09	−9.28 to 3.48	89.6	0.63
≥16	35	1.93	0.15 to 0.28	90.4		30	−4.64	−10.4 to 1.16	92.2	

BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WMDs, weighted mean differences.
**P* values for the impact of potential modifiers on the exercise effects.
†BMI in kg/m^2: obese ≥30; nonobese <30.
‡Health status: participants having at least 1 of type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndrome (yes) vs those with none of them (none).

Table 7. WMDs in Biomarkers of Glucose Intolerance and Insulin Resistance Comparing Exercise Intervention Groups to Control Groups by Specific Modifiers

	Fasting Glucose (mmol/L)					Fasting Insulin (μIU/mL)				
Modifier	n	WMD	95% CI	I^2, %	$P_{interaction}$*	n	WMD	95% CI	I^2, %	$P_{interaction}$
Age, y										
<50	5	0.09	−0.11 to 0.29	91.3	0.57	4	−1.34	−3.44 to 0.76	76.9	0.22
≥50	7	0.01	−0.06 to 0.07	36.9		3	0.45	−1.23 to 2.13	75.6	
Sex										
Women	16	−0.06	−0.19 to 0.08	91.4	0.93	9	−0.27	−1.12 to 0.57	68.7	0.04
Men	9	−0.07	−0.25 to 0.12	84.3		6	−2.86	−3.55 to −2.17	0.0	
Lifestyle										
Active	2	−0.20	−0.74 to 0.34	99.0	0.63	0	NA	NA	NA	NA
Sedentary	29	−0.06	−0.16 to 0.03	80.2		17	−0.94	−1.75 to −0.13	78.5	
BMI†										
Obese	20	−0.06	−0.20 to 0.07	90.7	0.90	13	−0.93	−2.18 to 0.32	82.0	0.88
Nonobese	18	−0.05	−0.17 to 0.07	80.7		10	−0.86	−1.52 to −0.19	32.8	
Health status‡										
Yes	9	−0.18	−0.40 to 0.05	0.0	0.40	6	−2.68	−4.67 to −0.70	75.2	0.05
None	27	−0.03	−0.11 to 0.06	87.2		14	−0.70	−1.60 to 0.21	77.5	
Duration, wk										
<16	30	−0.10	−0.22 to 0.03	90.0	0.70	13	−1.35	−2.50 to −0.20	79.3	0.58
≥16	19	−0.02	−0.09 to 0.06	47.5		16	−0.83	−1.83 to 0.17	78.7	

BMI indicates body mass index; NA, not available due to the lack of comparisons reported for active participants; WMDs, weighted mean differences.
**P*-values for the impact of potential modifiers on the exercise effects.
†BMI in kg/m^2: obese ≥30; nonobese <30.
‡Health status: participants having at least 1 of type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndrome (yes) vs those with none of them (none).

of the notion that, in addition to modifying total cholesterol and LDL-C, exercise training may also affect cardiovascular health through other pathways. We found that people in exercise groups also had significantly lower levels of IL-18 and several biomarkers of insulin resistance and hemostatic factors, indicating that exercise may exert its effects via pathways of inflammation-characterized atherothrombosis and insulin resistance. A recent review suggested that exercise training may regulate white adipose tissue mass and the expression of adipokines.[210] Obesity has become widely regarded as a chronic proinflammatory state, and substantial evidence indicates that chronic inflammation in adipose tissues, especially in white adipose tissue, could lead to insulin resistance.[211,212] Consequently, it is biologically plausible that by reducing the white adipose tissue mass and regulating the expression of adipokines, exercise could mitigate the chronic inflammation in adipose tissues, resulting in improved insulin sensitivity. Nevertheless, the exact mechanism remains to be elucidated.

The results from the subgroup analyses also may have important clinical implications. Consistent with previous evidence,[213] both moderate and vigorous exercise training appeared to have favorable effects on cardiorespiratory fitness and cardiometabolic health. We found that the differences in CVD risk between exercise groups and control groups were not significantly modified by lifestyle, body mass index, or intervention duration. These findings suggest that exercise interventions may have similar effects on cardiovascular health in populations regardless of these factors. Alternatively, the effectiveness of exercise training appeared to be different across strata of age, sex, and health status. The effects of exercise interventions on CRF measures were modified by age, sex, and health status such that people aged <50 years, men, and people with type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndrome appeared to benefit more from exercise interventions. We also observed significant modification of the effects on total cholesterol and LDL-C by preexisting medical conditions (type 2 diabetes, hypertension, hyperlipidemia, or metabolic syndromes), and that may explain why we did not find significant effects of exercise on total cholesterol and LDL-C. This finding also suggests that exercise interventions may provide significant benefits for people with those preexisting conditions by lowering total cholesterol and LDL-C.

Table 8. WMDs in Cardiorespiratory Fitness and Circulating Concentrations of Biomarkers Comparing Moderate and Vigorous Exercise Intervention Groups to Control Groups

	Moderate			Vigorous		
Outcome	No.*	WMD	95% CI	No.*	WMD	95% CI
Cardiorespiratory fitness						
Absolute, L/min	39	0.22	0.16 to 0.29	33	0.31	0.22 to 0.40
Relative, mL/kg per minute	64	3.22	2.61 to 4.18	68	3.26	2.63 to 3.89
Lipids markers						
TC, mg/dL	41	4.25	−7.73 to 16.6	28	3.87	−31.7 to 39.8
TG, mg/dL	37	−5.31	−12.4 to 1.77	32	−5.31	−11.5 to 0.09
HDL-C, mg/dL	44	1.16	−0.39 to 2.71	33	2.71	0.39 to 5.03
HDL_2-C, mg/dL	2	1.16	−0.77 to 3.48	2	1.55	−1.16 to 4.25
HDL_3-C, mg/dL	1	−1.16	−5.80 to 3.87	2	0.04	−1.55 to 1.55
LDL-C, mg/dL	35	−3.09	−8.12 to 2.32	26	−4.64	−12.0 to 2.32
VLDL-C, mg/dL	5	−1.93	−5.41 to 1.93	2	−7.35	−22.9 to 6.19
Apo AI, g/L	4	0.03	0.02 to 0.04	1	0.00	−0.12 to 0.12
Apo AII, g/L	1	−0.001	−0.24 to 0.24	1	0.01	−0.01 to 0.03
Apo B, g/L	3	0.01	−0.01 to 0.03	2	−0.02	−0.21 to 0.18
FFA, mmol/L	5	−0.06	−0.16 to 0.03	3	−0.04	−0.17 to 0.10
Inflammatory markers						
CRP, mg/L	9	−0.23	−1.01 to 0.55	4	0.04	−0.24 to 0.31
IL-6, pg/mL	5	0.02	−0.22 to 0.25	2	−0.39	−0.83 to 0.06
IL-18, pg/mL	1	14.0	−128 to 156	1	18.4	0.02 to 36.8
TNF-α, pg/mL	3	0.06	−0.48 to 0.60	1	−0.01	−0.93 to 0.91
Adiponectin, μg/mL	1	3.52	1.17 to 5.87	6	0.52	−0.20 to 1.23
Leptin, ng/mL	1	−0.70	−1.19 to −0.21	6	−2.56	−4.04 to −1.08
Insulin resistance markers						
Glucose, mmol/L	31	−0.04	−0.24 to 0.17	22	0.03	−0.08 to 0.12
Insulin, μIU/mL	17	−0.91	−2.08 to 0.26	17	−1.32	−2.15 to −0.50
HOMA-IR	7	−0.30	−0.66 to 0.06	7	−0.47	−0.82 to −0.12
HbA1c, %	11	−0.28	−0.46 to −0.11	7	−2.71	−0.54 to −0.002
C-peptide, nmol/L	1	0.22	0.19 to 0.25	1	−0.18	−0.62 to 0.26
IGF-1, ng/mL	2	−4.64	−29.58 to 20.30	3	3.91	−2.87 to 10.69
IGF-BP3, μg/mL	0	NA	NA	2	−0.002	−0.23 to 0.23
Hemostatic factors						
Fibrinogen, g/L	0	NA	NA	2	−0.39	−0.75 to −0.03
Endothelin-1, pg/mL	2	−0.22	−0.62 to 0.19	0	NA	NA
Angiotensin II, pg/mL	2	−1.32	−2.11 to −0.54	0	NA	NA

Apo AI indicates apolipoprotein A1; Apo AII, apolipoprotein A2; Apo B, apolipoprotein B; CRP, C-reactive protein; FFA, free fatty acid; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; IGF-1, insulin-like growth factor 1; IGF-BP3, insulin-like growth factor binding protein 3; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; NA, not available due to the lack of comparisons reported; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor α; VLDL-C, very low-density lipoprotein cholesterol; WMDs, weighted mean differences.
*Number of eligible independent comparisons.

Strengths of this meta-analysis include the comprehensive and systematic review of both conventional and novel CVD biomarkers, detailed subgroup analyses for potential effect modifiers that have not been conducted previously, assessment of robustness with regard to exercise intensity, and evaluation of the risk of different bias. The 2008 Physical

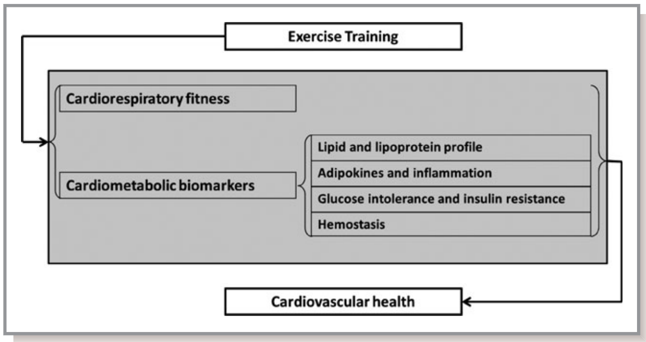

Figure 4. Mechanisms by which exercise training may improve cardiovascular health.

Activity Guidelines Advisory Committee Report included a number of comprehensively systematic reviews and meta-analyses based mostly on observational studies.[214] The evidence from RCTs has been relatively scarce, especially for novel cardiometabolic biomarkers. Our study is the first that synthesized evidence from the RCT setting and covered a comprehensive set of both traditional and novel biomarkers. Our findings are corroborated by several previous meta-analyses of RCTs,[20,215] but the inclusion of both sexes, more studies, subgroup analyses, and sensitivity analyses allowed us to achieve higher precision in the estimates and to determine the effect modification in subgroups.

This meta-analysis had some limitations. First, the evidence for hemostatic factors is based on a limited number of available trials, and we were not able to synthesize evidence for some novel biomarkers, such as plasminogen activator inhibitor 1, lipoprotein(a), and homocysteine due to sparse available data. Second, subgroup analyses were restricted to outcomes with >20 studies included, and cutoff points used for categorizing modifiers were arbitrarily selected. Third, due to the heterogeneity of exercise training programs and the limited number of RCTs that provided separate data, this meta-analysis can neither perform a dose-response analysis nor distinguish exercise types. We maximized the utility of data regarding exercise duration and intensity available from original RCTs and found that exercise effects were not significantly different across subgroups defined by duration and intensity. Our findings are consistent with previous evidence showing that both moderate and vigorous exercise training has similarly favorable effects on cardiometabolic health.[213] The duration threshold at which exercise exerts its effects needs further investigation. Fourth, to maintain independence, we selected 1 comparison from each trial with exercise groups of different intensities compared with 1 single control group. The results may potentially be subject to bias by excluding several eligible intervention groups with moderate intensity; however, we found that the direction and magnitude of the effects on most of the outcome measures were quite similar between moderate and vigorous interventions (Table 8). Finally, like any meta-analysis, our results may be prone to publication bias and inherent weaknesses of individual studies.

In conclusion, this large meta-analysis of RCTs clearly shows that exercise training significantly improved CRF and some traditional and novel CVD biomarkers in adults without CVD, indicating the causal role of exercise in the primary prevention of CVD morbidity and mortality.

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Author contributions: Lin, Liu, and Song designed research; Lin and Zhang were involved in data collection; Lin analyzed data; Guo, Roberts, McKenzie, Wu, and Liu participated in interpretation of findings; Lin and Song wrote the first draft. All authors read, edited, and approved the final manuscript.

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Disclosures

None.

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