Comparison of the Cardiovascular Benefits of Resistance, Aerobic, and Combined Exercise (CardioRACE): Rationale, design, and methods

Angelique G. Brellenthin, PhD,[a] Lorraine M. Lanningham-Foster, PhD,[b] Marian L. Kohut, PhD,[a] Yehua Li, PhD,[c] Timothy S. Church, MD, MPH, PhD,[d] Steven N. Blair, PED,[e] and Duck-chul Lee, PhD[a] *Ames, IA; Riverside, CA; Baton Rouge, LA; and Columbia, SC*

Background The benefits of aerobic exercise (AE) for cardiovascular disease (CVD) have been well documented. Resistance exercise (RE) has been traditionally examined for its effects on bone density, physical function, or metabolic health, yet few data exist regarding the benefits of RE, independent of and combined with AE, for CVD prevention. This randomized controlled trial, "Comparison of the Cardiovascular Benefits of Resistance, Aerobic, and Combined Exercise (CardioRACE)," is designed to determine the relative benefits of RE, AE, or combined RE plus AE training on CVD risk factors.

Methods Participants are 406 inactive men and women (35-70 years) with a body mass index of 25-40 kg/m^2 and blood pressure (BP) of 120-139/80-89 mm Hg without taking antihypertensive medications. Participants are randomly assigned to RE only, AE only, combined RE and AE (CE), or a no exercise control group. Participants perform supervised exercise at 50%-80% of their relative maximum intensity for both AE and RE, 3 times a week for 60 minutes per session, for 1 year (all 3 groups are time matched).

Results The primary outcome is a composite *z* score including resting BP, low-density lipoprotein cholesterol (LDL-C), fasting glucose, and percent body fat, which is assessed at baseline, 6 months, and 12 months. Diet and outside physical activity are measured throughout the intervention for 1 year.

Conclusion CardioRACE (ClinicalTrials.gov NCT03069092) will fill an important knowledge gap regarding the effects of RE, alone or in addition to the well-documented effects of AE. CardioRACE will help generate more comprehensive and synergistic clinical and public health strategies to prevent CVD. (Am Heart J 2019;217:101-11.)

One out of 3 deaths is caused by cardiovascular disease (CVD), and 1 out of 4 individuals in the United States (US) is currently living with some form of CVD.[1] The economic impact of CVD is estimated at $330 billion per year.[1] This will increase to an estimated $749 billion in 2035 because approximately half of the current adult population in the US has *high blood pressure* (BP), defined as a systolic/diastolic BP of ≥130/80 mm Hg according to 2017 guidelines.[1,2] There is an obvious need for well-defined lifestyle interventions, such as exercise and diet, to mitigate the rising costs and burdens associated with CVD.

Physical activity (PA), particularly aerobic exercises (AE) such as brisk walking or jogging, is well established as an effective method to prevent and treat CVD. The current federal Physical Activity Guidelines (PAG) state that adults should obtain at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic PA to significantly reduce their risk of CVD. There are also simpler guidelines to perform resistance exercise (RE), such as weight lifting, on ≥2 days per week.[3] RE provides bone, muscle, and metabolic health benefits; however, limited evidence of RE's efficacy, independent of and combined with AE, on CVD risk factors has precluded the development and

From the [a]Department of Kinesiology, Iowa State University, Ames, IA, [b]Department of Food Science and Human Nutrition, Iowa State University, Ames, IA, [c]Department of Statistics, University of California-Riverside, Riverside, CA, [d]Department of Preventive Medicine, Pennington Biomedical Research Center, Baton Rouge, LA, and [e]Department of Exercise Science, University of South Carolina, Columbia, SC.

RCT#: NCT03069092

Declarations of interest: none.

AcknowledgementsThis research is supported by the National Heart, Lung, and Blood Institute (R01HL133069).

Submitted April 24, 2019; accepted August 9, 2019.

Reprint requests: Dr Duck-chul Lee, Department of Kinesiology, Iowa State University, 103H Forker Bldg, 534 Wallace Rd, Ames, Iowa 50011-4008.

E-mail: dclee@iastate.edu

0002-8703

https://doi.org/10.1016/j.ahj.2019.08.008

dissemination of more precise guidelines surrounding RE. This discrepancy is reflected in reports indicating that approximately 50% of adults meet the AE guidelines, yet only 20% meet the RE guidelines, and even fewer meet both guidelines based on self-report.[4]

There is strong evidence that AE contributes to the improvements in known CVD risk factors including blood lipids, hemodynamics, and cardiorespiratory fitness.[5] There is also growing evidence that RE improves other CVD risk factors such as glucose metabolism, insulin sensitivity, and muscular strength and mass.[5] Other potential mechanisms by which RE prevents CVD are through improved weight management,[6] endothelial function,[7] and hemodynamics.[8,9]

Results from previous studies conducted in patients with metabolic dysfunction (eg, diabetes) have suggested that performing both AE and RE has greater benefits on metabolic health than performing either exercise alone.[10-12] However, most studies examining CVD biomarkers especially in healthy adults have had limitations including short intervention durations (8-12 weeks), sample sizes of less than 30 per group, lack of a control group, or having the combined exercise group workout for twice as long compared to AE- or RE-only groups.[13-17] Therefore, it is uncertain whether the added benefits of combined exercise simply reflect the extra exercise time performed by that group and if these benefits are sustainable in the long term.

"Comparison of the Cardiovascular Benefits of Resistance, Aerobic, and Combined Exercise" (CardioRACE) is being conducted to address the limitations of previous studies and to find the most effective type of exercise for CVD prevention. CardioRACE is a 1-year randomized controlled exercise intervention wherein 406 participants who are at risk of CVD were randomly assigned to 1 of 4 groups: (1) resistance exercise only (RE), (2) aerobic exercise only (AE), (3) combined resistance and aerobic exercise (CE), or (4) no exercise control (CON). The exercise groups are time matched (same exercise time) and engage in supervised exercise 3 times per week for 60 minutes each session for 1 year. Daily physical activity and dietary intake are monitored in all groups throughout the year. The primary outcome is a composite z score calculated using well-established traditional CVD risk factors including resting BP, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and percent body fat, which represent hypertension, hypercholesterolemia, diabetes, and obesity, respectively, which are all well-documented major CVD risk factors.[18,19] We also plan to investigate each CVD risk factor separately, especially BP, because all participants have elevated or high BP at baseline. In addition, we will explore other traditional and emerging CVD risk factors and biomarkers such as cardiorespiratory fitness, muscular strength, central hemodynamics (eg, central blood pressure and arterial stiffness), and >40 different inflammatory markers. All these outcomes are measured at baseline, 6 months, and 12 months. The primary aim of CardioRACE is to evaluate the independent and additive (combined) effects of RE and AE training on overall CVD risk factors. Specifically, we hypothesize that RE-only and AE-only will have independent beneficial effects on composite z scores through different pathways compared with the CON and that CE training will have a greater additive improvement on composite z scores compared with either RE or AE alone.

Busy middle-aged adults report that they have no time to exercise.[20] The simple message from CardioRACE, a time-matched exercise intervention, could be that replacing half of their normal AE with RE, rather than doubling their exercise time by adding more RE, produces larger and more comprehensive total CVD benefits. However, regardless of its findings, CardioRACE will expand our understanding of the roles of RE, independent of and combined with AE, for CVD prevention. Furthermore, this study will address an important gap surrounding the potential mechanisms underlying RE's effects, apart from or in combination with the well-documented effects of AE, on various traditional and emerging CVD risk factors.

Methods

Participants

CardioRACE completed recruitment and enrollment of 406 adults in year 3 of the study, but the exercise intervention and outcomes' assessments are currently ongoing. At baseline, participants were inactive, nonsmoking men and women between 35 and 70 years old who were overweight or obese (body mass index [BMI] of 25-40 kg/m^2) with elevated or high BP (resting systolic BP [SBP] of 120-139 mm Hg or resting diastolic BP [DBP] of 80-89 mm Hg) but not taking antihypertensive medications. These individuals had at least 3 risk factors (overweight, inactive, elevated BP) for CVD and were thus expected to gain the most cardiovascular benefits from this study.[21] Although individuals with stage II hypertension (≥140/90 mm Hg) were excluded considering the safety of the study, participants with controlled diabetes (hemoglobin A1c ≤7.0%) or hypercholesterolemia were included for the generalizability. Individuals with elevated BP (120-139/80-89 mm Hg) are more likely to have comorbid conditions such as diabetes or high cholesterol, so including these conditions increases the generalizability of the results to the large segment of the population who have elevated BP or stage I hypertension.

All participants were willing and able to provide written informed consent. The study was approved by the local institutional review board and is registered at www.clinicaltrials.gov (ID: NCT03069092). The inclusion and exclusion criteria for CardioRACE are listed in Table I.

Recruitment and screening procedures

CardioRACE recruited community-dwelling adults who mostly reside within 20 miles of the study center (Iowa State University in Ames, IA) because participants attend

Table I. Inclusion and exclusion criteria

Inclusion criteria:
- Men and women between 35-70 y old
- Nonsmoking
- BMI between 25 and 40 kg/m^2 (or BMI between 23 and 40 kg/m^2 for Asian individuals)
- Inactive (not meeting the aerobic and resistance exercise guidelines over the past 3 m)
- SBP of 120-139 mm Hg or DBP of 80-89 mm Hg
- Not on antihypertensive medications

Exclusion criteria:
- Significant cardiovascular disease such as:
  - Unstable coronary heart disease or decompensated heart failure
  - Severe pulmonary hypertension, aortic stenosis, or uncontrolled arrhythmias
  - Acute myocarditis, endocarditis, pericarditis, or aortic dissection
  - Previous myocardial infarction or stroke
  - Pacemaker or other implanted device
- Other medical conditions that are life-threatening or that can interfere with or be aggravated by the exercise training such as:
  - Cancer requiring treatment in the past 5 y
  - Autoimmune diseases
  - Uncontrolled diabetes mellitus (hemoglobin A1c >7.0%)
  - Severe arthritis or mobility limitations
- Severe depression (Beck Depression Inventory-II Score ≥29)
- > 4 wk of travel planned during the intervention period
- Unexplained or irregular weight loss or gain of more than 5% body weight over the previous 6 m
- Women who are pregnant or who plan to become pregnant in the next year

supervised exercise sessions at the center 3 times per week for 12 months. Recruitment strategies included attending health fairs and community events; providing health screenings to local businesses and organizations; working with local human resources professionals and worksite wellness coordinators; posting recruitment materials throughout the community, in health clinics, and on campus; advertising through local media outlets; emailing listservs; and mailing recruitment materials to households within the recruitment radius.

Interested individuals were provided information about the study and were screened for initial eligibility criteria (ie, age, medication use, height, weight, physical activity, disease status) through either telephone screening or information sessions that were open to the public. Eligible participants were then invited to an orientation session where they learned more about the study, provided informed consent, and completed additional screening measures including medical history and physical activity readiness questionnaires, as well as height, weight, and BP assessments.

Following the orientation visit, participants visited the testing center for 5 education sessions to learn about general health education topics as well as study-specific protocols before baseline assessment. BP as an inclusion criterion was assessed during the orientation and the first 3 education visits. A series of 4 BP measurements in each visit was collected with a 1-minute rest between readings. The 4 readings were averaged, and at least 2 of the 4 visits had to meet SBP and DBP inclusion criteria for participants to proceed to the remaining 2 visits. After the run-in period, participants completed 2 days of baseline medical assessments and were then randomized to their study groups. See Figure 1 for a diagram of the participant flow from screening to randomization.

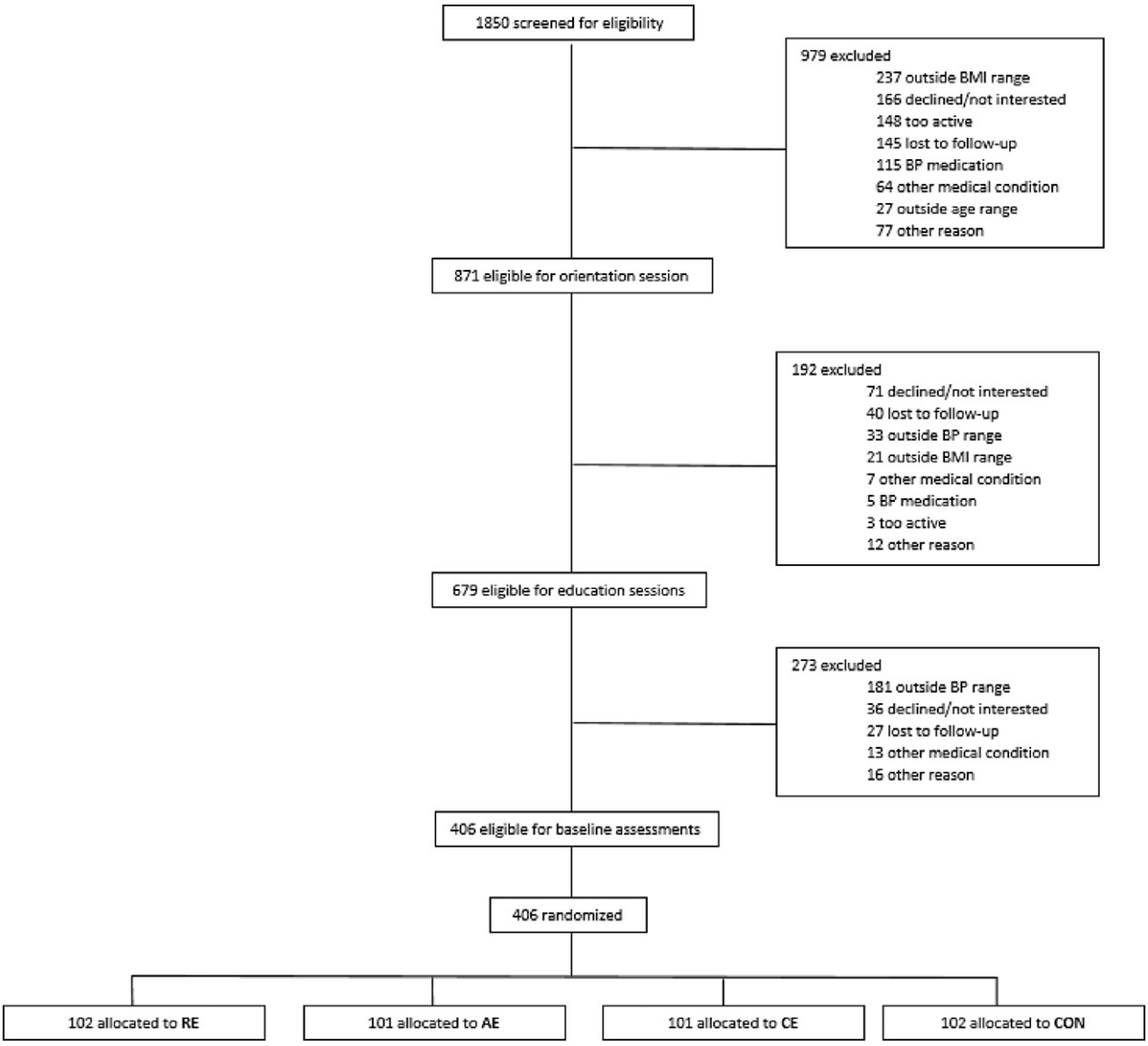
CardioRACE screened 1,850 interested individuals and randomized 406 participants into experimental groups (102 into resistance, 101 into aerobic, 101 into the combination, and 102 into the control). The baseline characteristics of the study participants are depicted in Table II. There were no significant group differences in the main eligibility criteria at baseline (all $P > .05$). However, interim data analyses are not allowed in this study, so full baseline characteristics including all outcome variables will be provided after completing the study.

Study outcomes

The primary outcome is the change from baseline to 12-month follow-up in the composite CVD risk score (z score) calculated using resting BP, LDL-C, fasting glucose, and percent body fat. These 4 variables represent primary modifiable CVD risk factors included in the atherosclerotic CVD (ASCVD) risk algorithm developed by the American Heart Association (AHA) and American College of Cardiology.[22,23] In addition, these factors represent the 4 major modifiable health conditions—hypertension, hypercholesterolemia, diabetes, and obesity—identified by the AHA, American College of Cardiology, and Centers for Disease Control and Prevention that increase the risk for CVD.[23-25]

In general, individuals at high risk of developing CVD have a cluster of risk factors influenced by numerous physiological systems and functions (eg, hemodynamics, blood lipids, glucose metabolism, and adiposity) rather than a single risk factor. Therefore, overall CVD risk score, which quantifies and predicts future CVD risk, is widely used from both clinical and public health perspectives (eg, Framingham CVD risk score) in CVD prevention.[26] Most people will likely show significant improvements in some but not all CVD risk factors, and the combination of improvements will vary between individuals. Thus, focusing on a single CVD risk factor may not fully explain the cumulative or comprehensive benefits of exercise that can affect multiple physiological systems and functions. The composite CVD risk score is especially useful when comparing the total effectiveness of different types or combination of exercise. For example, AE has been shown to improve hemodynamics (eg, blood pressure) and blood lipid profile (eg, LDL-C) to a greater degree than RE, but RE might be relatively more beneficial for improving glucose metabolism (eg, fasting

Figure 1



Participant flow from initial screening to randomization.

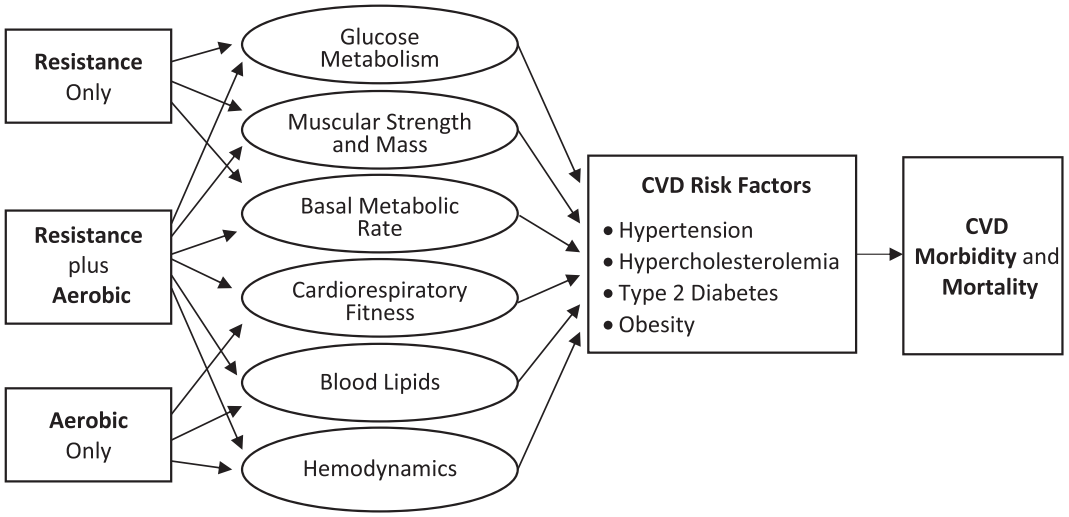
Table II. Baseline eligibility characteristics of the study participants by experimental group

Variable	All	Resistance	Aerobic	Combination	Control	*P* value
n	406	102	101	101	102	
Female, n (%)	216 (53)	53 (52)	53 (52)	55 (54)	55 (54)	.98
Racial or ethnic minority, n (%)*	85 (21)	22 (22)	21 (21)	21 (21)	21 (21)	1.00
Age (y)	50.3 (9.9)	49.8 (10.4)	50.3 (9.8)	50.5 (9.5)	50.4 (9.8)	.96
BMI (kg/m^2)	31.2 (4.9)	31.5 (5.2)	31.2 (4.8)	31.1 (5.0)	31.2 (4.8)	.94
SBP (mm Hg)	126.0 (11.2)	126.0 (11.2)	125.9 (10.3)	126.6 (11.6)	125.5 (11.7)	.88
DBP (mm Hg)	81.7 (8.2)	82.2 (7.8)	81.4 (8.1)	82.1 (8.9)	81.1 (8.1)	.62

Data are presented as mean (SD) unless indicated otherwise. Baseline group differences in continuous variables analyzed using 1-way ANOVA; categorical variables analyzed using χ^2 tests.

*Participants identifying as American Indian or Alaska Native, Asian, black or African American, Hispanic or Latino, and/or Native Hawaiian or other Pacific Islander.

Figure 2



Mechanistic pathway between resistance, aerobic, or combined exercise training and CVD

glucose) and body composition (eg, muscle mass and percent body fat) as depicted in Figure 2. However, there is very little evidence, and we still do not know what type or combination of exercise is best for the prevention of the clinical outcome of CVD such as heart attack or stroke instead of its single risk factor (eg, hypertension or diabetes). The composite score in CardioRACE will inform what type or combination of time-matched exercise is comparatively most effective for improving the overall CVD risk profile in middle-aged adults who are at high risk of developing CVD. We will also investigate the changes in each of these risk factors (resting BP, LDL-C, fasting glucose, and percent body fat) separately, as assessing individual CVD risk factors will be important to compare our results to previous studies that mostly focused on a single CVD risk factor (eg, blood pressure). Other outcomes of interest include changes in emerging CVD risk factors such as arterial stiffness, cardiorespiratory and muscular fitness, inflammatory markers, waist circumference, body composition (eg, muscle mass), and bone mineral density.

Assessment day 1. All outcomes are assessed over 2 study visits at baseline, 6 months, and 12 months. Day 1 occurs in the morning after a minimum 12-hour fast during which participants do not drink or eat anything besides plain water. Participants are also instructed to avoid exercise and alcohol within 48 hours of the appointment. Participants do not take over-the-counter medications within 24 hours or prescription medications the morning of the visit.

Lifestyle and psychosocial factors are assessed with a detailed questionnaire. Variables assessed include demographics, medical history, medication use, physical activity, smoking, alcohol intake, health-related quality of life (36-Item Short Form Health Survey),[27] stress (Perceived Stress Scale),[28] depression (Beck Depression Inventory-II),[29] anxiety (Trait Anxiety Inventory),[30] and sleep quality (Pittsburgh Sleep Quality Index).[31]

Peripheral SBP and DBP are measured following a minimum of 10 minutes of seated rest using the Omron HEM-907xl automated digital BP monitor (Omron Healthcare, Inc, Lake Forest, IL). Following AHA guidelines,[2] participants are instructed to not talk and to sit back comfortably in the chair with their lower back supported and feet uncrossed during readings. A brachial pressure cuff is placed around their supported left arm at the level of the atria. The research assistant exits the room, and the BP device takes 3 measurements with 2 minutes of rest between each BP measurement.

Central SBP and DBP, resting heart rate (HR), and arterial stiffness are assessed using the SphygmoCor XCEL (AtCor Medical, Itasca, IL) automated oscillometric device. Central BP and resting HR are assessed following the same procedures as peripheral BP except that the participant is in the supine position instead of seated. Arterial stiffness is assessed via carotid-femoral pulse wave velocity following the AHA recommended guidelines.[32]

Anthropometric measurements are taken without shoes and in laboratory-provided attire (scrubs). Height (m) and weight (kg) are assessed using a standard stadiometer and digital scale (SECA 769, Hamburg, Germany), respectively. Waist circumference (cm) is measured against the skin at the level of the umbilicus using inelastic tape. Height, weight, and waist circumference measurements are performed in duplicate, and the average value is used. Body composition, including fat mass, muscle mass, bone mineral density, and percent

body fat, is measured using the Hologic Horizon dual x-ray absorptiometry machine (Hologic, Inc., Marlborough, MA) following standard procedures.[33]

Blood chemistry, including blood lipids and lipoproteins (total, high-density, and LDL-C, and triglycerides), fasting glucose and insulin, hemoglobin A1c, and >40 inflammatory markers (eg, cytokines, chemokines, and growth factors), is analyzed using blood collected from the antecubital vein after a minimum 12-hour overnight fast.

Assessment day 2. Day 2 occurs in the afternoon because it involves nonfasted physical fitness tests. Like day 1, participants are instructed to avoid exercise and alcohol within 48 hours of the appointment.

Following the same procedures described above, peripheral SBP and DBP are also measured during day 2 to account for day-to-day and time-of-day variability as well as fasted versus nonfasted status. The mean BP from day 1 and the mean BP from day 2 are averaged to calculate BP at baseline, 6 months, and 12 months.

Physician-supervised cardiorespiratory fitness (VO_{2max}) is assessed using a maximal graded treadmill test based on the Balke and Ware protocol, which is considered valid and safe for high-risk participants.[34] Participants were familiarized with the testing procedures during one of the run-in sessions. Following the American College of Sports Medicine's guidelines for exercise testing, participants wear an HR monitor (Polar, Lake Success, NY) and expire through a tube attached to a Physio-dyne Max-TT metabolic cart (Fitness Instrument Technologies, Quogue, NY).[35] The grade increases by 1% per minute with the speed fixed at 88 m/min (3.3 mph) until volitional fatigue.[34] HR and gas exchange variables including VO_2, CO_2, ventilation, and respiratory exchange ratio are recorded every 30 seconds. Perceived exertion using the Borg 6-20 scale is assessed every other minute and at volitional fatigue. Valid VO_{2max} values will be identified using American College of Sports Medicine criteria (eg, respiratory exchange ratio ≥1.1, plateau in VO2 or HR with increasing workload, rating of perceived exertion >17) and considered in analyses of cardiorespiratory fitness.

Muscular strength is determined for both upper and lower body by a 1-repetition maximum (1-RM) protocol using the chest and leg press machines (Technogym, Gambettola, Italy), respectively, following the National Strength and Conditioning Association guidelines.[36] Participants perform 3 warm-up sets of 10, 5, and then 2-3 repetitions of successively higher weights separated by 2 minutes of rest each. Participants then perform a series of 1-RM attempts in 5- to 10-lb increments, with 2-4 minutes of rest between trials. The final maximal weight lifted successfully is considered the participant's absolute 1-RM. Grip strength is assessed using a digital hand dynamometer (Jamar Plus+; Patterson Medical, St Paul, MN). Participants sit in a chair with their arm at their side and elbow at a 90° angle. Participants perform 3 maximal contractions separated by 30 seconds for both the left and right hands, and the average of the highest value from each hand is used. However, other methods (eg, the highest, average from all tests) will also be considered because there is no universal consensus.

Randomization

Following baseline assessments, eligible participations are randomized. The randomization sequence was generated by the study statistician using a computer program. Randomization follows a stratified block design using sequences of permuted blocks of equal length that contained the treatment assignments (RE, AE, CE, or CON) in random order. The predefined strata were based on sex (male or female), race/ethnicity (non-Hispanic white or all other races and ethnicities), age (35-44, 45-54, 55-64, or 65-70 years), and baseline BMI (<30, 30-34, or 35-40 kg/m^2). Group allocations are concealed in opaque envelopes that are opened by participants in front of intervention staff during a separate study visit.

Masking procedures

All assessment staff are separated from the exercise intervention. The assessment team is blinded to the group assignments and consists of study staff who conduct and collect all baseline and follow-up data. Participants are instructed to not reveal their group assignment to the assessment team during testing. In addition, the primary CVD-related outcomes of the study such as BP and blood lipids are assessed using an automated BP monitor or are analyzed by an independent laboratory (Quest Diagnostics, Secaucus, NJ), respectively, which greatly reduces the potential for human error or bias. The data manager is also blinded to group assignments, and double entry of data is performed to check for accuracy. The exercise intervention team consists of staff members who communicate directly with participants and who prescribe, track, and supervise exercise following the preprogrammed, computer-controlled, standardized exercise prescription in each exercise group. They are not involved in outcomes' assessment or data entry.

Exercise interventions and control

The RE, AE, or CE interventions are matched for time (180 min/wk) and frequency (3 d/wk for 60 minutes each session including 50 minutes of RE, AE, or CE and 5 minutes each of warm-up and cool-down exercises). The 2018 PAG recommend 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity AE per week (equal to ≥500 MET-min/wk), and ≥2 days of RE per week.[3] In CardioRACE, the RE training meets the RE guidelines only, the AE training meets the AE guidelines only, and the combined RE plus AE training meets both guidelines. The guidelines provide more detailed recommendations for AE yet provide relatively simple guidelines for RE partly because of limited evidence and

Table III. Exercise parameters for each group

Group	Frequency	Duration	Intensity	Type
Resistance	3 times per week	60 min	3 sets of 12 exercises at 50%-80% 1-RM	Leg press, hamstring curl, quadriceps extension, hip abduction, chest press, lat pulldown, shoulder press, biceps curl, triceps extension, abdominal crunch, lower back extension, and torso rotation
Aerobic	3 times per week	60 min	50%-80% heart rate reserve	Upright or recumbent bike, elliptical, and treadmill
Combination	3 times per week	60 min (30 min aerobic plus 30 min resistance)	Resistance: 2 sets of 9 exercises at 50%-80% 1-RM Aerobic: 50%-80% heart rate reserve	Resistance: Leg press, hamstring curl, quadriceps extension, chest press, lat pulldown, abdominal crunch, lower back extension, and torso rotation Aerobic: Upright or recumbent bike, elliptical, and treadmill
Control	No exercise training			

difficulty of accurately tracking and reporting RE data (eg, intensity), especially in observational studies.

All exercise sessions are supervised by senior staff members and trained research assistants to encourage participants to complete the sessions, provide feedback, and supervise the actual training. However, exercise prescriptions are delivered through and automatically recorded using the Technogym Wellness System (Technogym, Gambettola, Italy). Each participant is assigned a key that stores their unique, individualized workout prescription that is programmed by staff considering their fitness levels and progression. Participants check in using their key at a computer kiosk, which records attendance automatically. After checking in, the participant inserts their key into each exercise machine, and their workout prescription is loaded onto the machine (eg, treadmill speed and grade are automatically controlled and adjusted following the stored exercise program in their key and each participant's HR during exercise). After each exercise, workout performance data (eg, HR, duration, sets, repetitions, pounds lifted) are stored in the key. Participants check out with their key, and their exercise data are transmitted back to the local database that follows confidentiality and safety regulations based on the study Institutional Review Board and Data Safety and Monitoring Board protocols. Staff help ensure the safety of the participants, their compliance with the exercise prescriptions, and accurate transmission of exercise data to servers. Staff also communicate directly with participants at each session to improve adherence and update exercise prescriptions as fitness levels change. With this detailed exercise data from a 12-month intervention, it will be possible to provide specific details regarding exercise parameters for various CVD-related biomarkers as described earlier,[37] which will better inform future physical activity recommendations for both resistance and aerobic exercise. This is a novel strength of the study for accurate exercise data collection as well as exercise attendance and compliance calculation, which is important for the interpretation of the outcome data between groups and individuals.

Resistance exercise. The RE group performs 3 sets of 8-16 repetitions at 50%-80% of 1-RM on each of 12 machines (see Table III for a list of the machines). In the first 8 weeks of the program, participants perform more repetitions (16-20) at a lower weight (30%-40% of 1-RM) for fewer sets (1-2 sets) to become familiar with the exercise program and to prevent potential injuries and severe muscle soreness. Participants rest a minimum of 1 minute between sets and between different machines. Strength is reevaluated every 8 weeks using estimated 1-RM protocols so that exercise prescriptions are continuously updated throughout 1 year. These continuous individualized strength evaluation and progressive prescription are important to prevent a possible decrease in CVD benefits at later months that is commonly observed in most exercise intervention studies.

Aerobic exercise. Aerobic prescriptions are based on 50%-80% of heart rate reserve (HRR) following a gradual progression in duration (20-50 minutes) and intensity throughout the first 8 weeks. Maximum HR (from the treadmill test) and resting HR from baseline assessments are used for AE prescriptions. Resting HR is reassessed every 8 weeks so that HRR prescriptions can be continuously updated throughout 1 year. Each session, participants have their choice of performing aerobic exercise on 2 machines (2, 25-minute segments) including upright or recumbent bicycles, elliptical machines, or treadmills. Participants wear an HR monitor (Polar, Lake Success, NY), and HR prescriptions are assigned to the participant's Technogym key. The Technogym key communicates with each machine to adjust the speed, grade, and/or resistance on the aerobic equipment to keep participants within the prescribed HR range, which is programmed to gradually increase from 50% to 80% HRR.

Combination exercise. CE is matched for time with the RE and AE groups (3 times per week for 60 minutes each time); however, the RE and AE training protocols are truncated by half so that participants perform 2 sets instead of 3 sets at the same intensity (50%-80% 1-RM) on 9 machines instead of 12 machines and 25 minutes of aerobic exercise at the same intensity (50%-80% HRR). As with the RE and AE protocols, muscular strength and

resting HR are reevaluated every 8 weeks to update the RE and AE prescriptions throughout 1 year.

Control group. The delayed exercise group serves as the control group. They do not perform exercise at the study center during the first 12 months of their participation, but they are offered their choice of RE, AE, or CE for 12 months (in year 2) after their first year of no exercise to help prevent dropout, which can occur more often in a no exercise control group. Any data collected from the control group's optional year of exercise (in year 2) will not be included in the primary data analyses described in this paper. Because the primary outcomes are predominantly physiological (eg, blood pressure and cholesterol) rather than psychological (eg, depression and quality of life), we chose not to use a more involved control group design (eg, health education classes, stretching), which may better control for the potential effects of human interaction on the outcomes. Furthermore, it was not clear what the effects of a year of health education or stretching would be on the variety of primary and secondary outcomes in CardioRACE, making it difficult to interpret the results of exercise training. To increase staff contact during their first 12 months of participation when they are not exercising, control group participants receive diet education and in-person counseling (described below) and communicate with staff at least weekly. See Table III for an outline of exercise prescriptions for each group.

Dietary counseling and monitoring

Participants in all 4 groups receive Dietary Approaches to Stop Hypertension (DASH) diet education during the run-in period and have individual dietary counseling appointments with a registered dietitian at 3, 6, 9, and 12 months throughout the intervention. The DASH is an evidence-based heart-healthy diet plan that recommends reducing sodium intake to <2300 mg/d while increasing intake of magnesium, potassium, and calcium. DASH also recommends consuming fruits and vegetables, whole grains, lean protein and meat, fat-free or low-fat dairy, and nuts and seeds, which is largely consistent with the Dietary Guidelines for Americans.[38] Participants complete an automated, computer-based 24-hour food recall on 3 random days per month (2 weekdays [Monday-Thursday] and 1 weekend day [Friday-Sunday]) throughout the 12 months. Dietary intake data are collected and analyzed using the Automated Self-Administered 24-hour Dietary Assessment Tool, version (2016, 2018), developed by the National Cancer Institute, Bethesda, MD.[39] During the individual diet counseling sessions, participants review their past food recalls and set dietary goals with the dietitian. Most exercise intervention studies focused solely on the effects of exercise without considering the benefits of diet counseling. However, considering both exercise and diet is a more effective and comprehensive behavioral approach from both clinical and public health perspectives and is a unique strength of the study. We provide the same diet counseling for all participants so that the difference in changes in outcome variables between groups is induced by exercise intervention only. In addition, the effect of DASH diet education on the outcome variables will be analyzed in the control group by comparing the pre- and postoutcome data.

Physical activity monitoring

Participants in all groups are instructed to not engage in structured aerobic or resistance exercise outside of the center throughout the duration of their participation. Participants are provided with a triaxial accelerometer-based pedometer (Omron HJ-321), which they wear during waking hours for the entire 12 months. Participants do not wear the pedometer during supervised exercise at the center. Daily step counts and wear times as well as participation in any muscle-strengthening activities are recorded weekly and checked by research staff. Exercise intervention studies often have measured outside lifestyle physical activity at the beginning and end of the intervention but not during the entire intervention period. This limitation may cause confounding bias because exercise study participants are highly motivated to be active outside the study center. In this study, we monitor total daily activity for all participants during the entire 1-year intervention using accelerometers.

Adherence and incentives

Completers are defined as participants who participate in both baseline and 12-month assessments, as these data collection points are included in the primary statistical analyses. *Dropouts* are defined as those who do not complete 12-month assessments. Because 100% adherence to the exercise protocol is unrealistic over a 1-year long period due to factors such as sickness, family obligations, and travel, CardioRACE defines acceptable adherence to the study protocol as completing ≥80% of the total amount of exercise prescribed in each group in this large (N = 406) clinical trial. If a participant has not reached ≥80% adherence by the end of the 12 months, they are given the option of completing up to another 4 weeks (extra 1 month) of exercise sessions prior to their final 12-month follow-up assessments following earlier studies.[11,40] Both completers and dropouts will be included in the primary intention-to-treat analyses, and the ≥80% attendance rate will be used to identify participants included in the treatment efficacy analyses. Also, we will consider other benchmarks (eg, 70% or 90% attendance) in additional analyses.

CardioRACE uses various strategies to minimize dropouts and maximize adherence. Similar to other extended exercise interventions, there was a month-long run-in period between the first study visit and the randomization visit.[10,40] Participants attended an orientation, 5

education sessions, and baseline assessments within a 5-week period to be eligible for randomization. These visits served several purposes including multiple measurement of BP to determine eligibility, instruction regarding study protocols (eg, how to use Automated Self-Administered 24-hour diet recall system), and ascertainment of the participant's ability to come to the center regularly. Throughout the exercise intervention, participants receive reports every 8 weeks on their attendance, average daily step counts, strength and/or resting HR changes, and total distance traveled (eg, from bike and treadmill) and/or weight lifted during their participation that are important to improve exercise and study compliance. They also receive birthday and holiday cards as well as monthly newsletters. CardioRACE incorporates motivational interviewing techniques during randomization and the 6-month assessment, behavioral contract signing, flexible exercise scheduling, and adherence monitoring to further improve study compliance. Participants receive an encouragement phone call, called an *I care call*, once per month from a staff member and are provided the opportunity to discuss their study experience and to problem solve any issues. Participants are also assigned 1 primary staff person as their principal contact ("CardioRACE coach") for study-related concerns. If a participant has 2 unexcused absences in a row, they are contacted by their exercise coach to discuss and find solutions to any potential barriers. Participants are expected to make up unexcused absences by coming to the center another time that week.

Each participant is given up to $300 as an incentive to complete the study. Participants are remunerated $60 for each baseline, 6-month, and 12-month assessment ($180). They receive an additional $60 at each the 6-month and 12-month assessment ($120) if they have provided at least ≥80% of their step counts and diet recalls in the previous 6 months.

Data analysis

Power computations were based on detecting a significant group-by-time interaction for the composite CVD risk z score (primary outcome) using a linear mixed effects model (4 groups × 2 times: baseline and 12-month follow-up) with $\alpha = .05$, power = 0.99, and a small to medium effect size (Cohen f effect size of 0.19) from an 8-week pilot study. It was estimated that 200 total participants (50 in each of the 4 groups) would be needed to observe significant group-by-time effects on the composite CVD score. To be able to further detect group differences in pairwise comparisons (eg, CE vs AE) and to account for anticipated participant attrition (an estimated 10%), diminished compliance over a 1-year intervention, as well as potential changes in confounding factors (eg, changes in medication, weight, or outside physical activity) over 1 year, the sample size was increased to 400, which was confirmed by the biostatistician of the study.

The primary outcome, the composite z score, will be the mean of the z scores of the 4 CVD risk factors: resting BP, LDL-C, fasting glucose, and percent body fat. Each risk factor will be individually standardized and expressed as a z score by using the formula = (value − mean)/SD for each participant. The means and SDs used to create the z scores for each risk factor at both baseline and follow-up will be the values from the entire sample at baseline. The primary outcome will be analyzed using the intention-to-treat principle and will include all participants as randomized. The potential effects of missing data will be explored through various imputation models and sensitivity analyses. We will also consider the effects of medications that affect LDL-C (eg, statins) or glucose (eg, insulin), which factor into the composite score. Analyses will take into account covariates including age, sex, BMI, and baseline values of each outcome measure. Linear mixed-effects models for repeated measures with effects for time (baseline and 12-month follow-up), experimental group, and group-by-time interaction will be used. If the P value for the group-by-time interaction is less than .05 (significant), we will adjust for multiple comparisons to estimate CIs and P values for the 6 prespecified intergroup contrasts: (1) RE versus CON, (2) AE versus CON, (3) CE versus CON, (4) CE versus RE, (5) CE versus AE, and (6) RE versus AE for changes in composite z scores and individual risk factors between baseline and 12-month follow-up. Additional analyses will examine treatment efficacy in the subgroup of adherent participants; evaluate treatment mediators (eg, changes in diet, medication, and weight during intervention); examine the sensitivity of results after omitting those with diabetes or lipid-lowering medications; assess the impact of incomplete data due to attrition; and examine treatment response at 6 months to evaluate the trends of exercise effects. Results from these additional analyses will be considered exploratory and will be interpreted with caution because of their inflation of the type I error rate. Data will be assessed for normality, and any skewed data could be transformed or analyzed nonparametrically. All P values will be 2-sided, and $P < .05$ will be considered statistically significant using SAS software version 9.4 (SAS Institute, Cary, NC).

This study is supported by the National Heart, Lung, and Blood Institute (R01HL133069). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Discussion

Cardiovascular disease is the leading cause of death in the US and is estimated to cause one third of deaths globally.[1,41] The 2018 PAG Advisory Committee Scientific Report stated that there was strong evidence demonstrating a significant inverse relationship between moderate

to vigorous intensity aerobic PA and incidence of CVD. However, as was the case in the first 2008 PAG Scientific Report 10years prior, there remain insufficient data to comment on the relationship between muscle-strengthening activities, independent of and combined with aerobic PA, and CVD-related outcomes.[42] There is a clear research need to delineate the unique and possibly additive benefits of RE alone or alongside traditional AE in the prevention of CVD, specifically for those who are at high risk.

In response, CardioRACE is an adequately powered, supervised, randomized controlled trial of exercise on CVD risk factors and biomarkers. CardioRACE will evaluate the effects of performing exercise meeting the RE guidelines only, the AE guidelines only, or both the RE and AE guidelines compared with a no-exercise control group. Important strengths of this study include (1) 1-year long exercise intervention with a comparative effectiveness (multifactorial) and exercise time-matched study design; (2) comprehensive and criterion-standard measurement of both traditional and emerging CVD risk factors such as BP, blood lipids, arterial stiffness, body composition, cardiorespiratory fitness, muscular strength, bone mineral density, and comprehensive inflammatory markers; (3) extensive monitoring of lifestyle factors such as diet (DASH) and lifestyle PA to control potential confounders throughout the 1-year intervention period; (4) precision and control over individual exercise programming and monitoring using an innovative computer-based exercise training system (Technogym Wellness System) to minimize a potential bias by research staff; (5) continuous and progressive adjustments for individualized exercise prescription (an increase of exercise intensity) to account for fitness changes every 2 months throughout the intervention; and (6) recruitment of 406 high-risk individuals with 3 known risk factors for CVD (overweight or obese, inactive, and elevated or high untreated BP) that has significant clinical and public health implication and impact. Following all these novel methodological approaches, we believe that this study will provide reliable and meaningful data, which can contribute to future physical activity recommendations.

Summary

CardioRACE will answer one of the most commonly asked questions about exercise and health—"What type and combination of exercise are most effective for cardiovascular benefits?"—by comparing the effects of RE, AE, and CE to improve a wide array of CVD risk factors among participants with established CVD risk factors. CardioRACE will yield evidence-based exercise data that can be used by both patients and clinicians, responding to the need for knowledge and information about exercise and CVD prevention.

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics 2018 update: a report from the American Heart Association. Circulation 2018, https://doi.org/10.1161/CIR.0000000000000558.
2. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2018;71(19):e127-248, https://doi.org/10.1016/j.jacc.2017.11.006.
3. U.S. Department of Health and Human Services. *Physical activity guidelines for Americans, 2nd edition*. Washington, DC: U.S. Department of Health and Human Services; 2018.
4. Carlson SA, Fulton JE, Schoenborn CA, et al. Trend and prevalence estimates based on the 2008 physical activity guidelines for Americans. Am J Prev Med 2010;39(4):305-13, https://doi.org/10.1016/j.amepre.2010.06.006.
5. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43(7):1334-59, https://doi.org/10.1249/MSS.0b013e318213fefb.
6. Jackson AW, Lee D-C, Sui X, et al. Muscular strength is inversely related to prevalence and incidence of obesity in adult men. Obesity 2010;18(10):1988-95, https://doi.org/10.1038/oby.2009.422.
7. Ashor AW, Lara J, Siervo M, et al. Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. Sport Med 2015;45(2):279-96, https://doi.org/10.1007/s40279-014-0272-9.
8. Cornelissen VA, Fagard RH, Coeckelberghs E, et al. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertens (Dallas, Tex 1979) 2011;58(5):950-8, https://doi.org/10.1161/HYPERTENSIONAHA.111.177071.
9. Zhang Y, Qi L, Xu L, et al. Effects of exercise modalities on central hemodynamics, arterial stiffness and cardiac function in cardiovascular disease: systematic review and meta-analysis of randomized controlled trials. Cavarretta E, ed. *PLoS One*. 2018;13(7):e0200829. doi:https://doi.org/10.1371/journal.pone.0200829.
10. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007;147(6):357-69http://www.ncbi.nlm.nih.gov/pubmed/17876019. Accessed August 28, 2018.
11. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin a $_{1c}$ levels in patients with type 2 diabetes. JAMA 2010;304(20):2253, https://doi.org/10.1001/jama.2010.1710.
12. Choo J, Lee J, Cho J-H, et al. Effects of weight management by exercise modes on markers of subclinical atherosclerosis and cardiometabolic profile among women with abdominal obesity: a randomized controlled trial. BMC Cardiovasc Disord 2014;14(1):82, https://doi.org/10.1186/1471-2261-14-82.
13. Bateman LA, Slentz CA, Willis LH, et al. Comparison of aerobic versus resistance exercise training effects on metabolic syndrome (from the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise—STRRIDE-AT/RT). Am J Cardiol 2011;108(6):838-44, https://doi.org/10.1016/j.amjcard.2011.04.037.
14. Timmons JF, Minnock D, Hone M, et al. Comparison of time-matched aerobic, resistance, or concurrent exercise training in older adults. Scand J Med Sci Sports July 2018, https://doi.org/10.1111/sms.13254.

15. Ho SS, Radavelli-Bagatini S, Dhaliwal SS, et al. Resistance, aerobic, and combination training on vascular function in overweight and obese adults. J Clin Hypertens 2012;14(12):848-54, https://doi.org/10.1111/j.1751-7176.2012.00700.x.
16. Sillanpää E, Laaksonen DE, Häkkinen A, et al. Body composition, fitness, and metabolic health during strength and endurance training and their combination in middle-aged and older women. Eur J Appl Physiol 2009;106(2):285-96, https://doi.org/10.1007/s00421-009-1013-x.
17. Wood RH, Reyes R, Welsch MA, et al. Concurrent cardiovascular and resistance training in healthy older adults. Med Sci Sports Exerc 2001;33(10):1751-8, http://www.ncbi.nlm.nih.gov/pubmed/11581562. Accessed August 28, 2018.
18. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. Circ Res 2016;118(11):1752-70, https://doi.org/10.1161/CIRCRESAHA.115.306883.
19. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012;366(4):321-9, https://doi.org/10.1056/NEJMoa1012848.
20. Trost SG, Owen N, Bauman AE, et al. Correlates of adults' participation in physical activity: review and update. Med Sci Sports Exerc 2002;34(12):1996-2001, https://doi.org/10.1249/01.MSS.0000038974.76900.92.
21. NHLBI. What are the risk factors for heart disease?, HHS, NIH, NHLBI. https://www.nhlbi.nih.gov/health/educational/hearttruth/lower-risk/risk-factors.htm. Accessed August 28, 2018.
22. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. Circulation 2014;129(25 suppl 2):S49-73, https://doi.org/10.1161/01.cir.0000437741.48606.98.
23. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol November 2018, https://doi.org/10.1016/j.jacc.2018.11.003.
24. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. Circulation 2010;121(4):586-613, https://doi.org/10.1161/CIRCULATIONAHA.109.192703.
25. CDC. Conditions that increase risk for heart disease |, cdc.gov. , https://www.cdc.gov/heartdisease/conditions.htm. Published 2019. Accessed July 11, 2019.
26. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117(6):743-53, https://doi.org/10.1161/CIRCULATIONAHA.107.699579.
27. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473–483. http://www.ncbi.nlm.nih.gov/pubmed/1593914.
28. Levenstein S, Prantera C, Varvo V, et al. Development of the perceived stress questionnaire: a new tool for psychosomatic research. J Psychosom Res 1993;37(1):19-32, https://doi.org/10.1016/0022-3999(93)90120-5.
29. Beck AT, Steer RA, Brown GK. *Beck depression inventory, second edition. Second.* Pearson: San Antonio, TX. 1996.
30. Spielberger CD, Gorsuch RL. *State-trait anxiety inventory for adults: sampler set: manual.* scoring key. Mind Garden: test. 1983.
31. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193-213, http://www.ncbi.nlm.nih.gov/pubmed/2748771. Accessed August 28, 2018.
32. Townsend RR, Wilkinson IB, Schiffrin EL, et al. Recommendations for improving and standardizing vascular research on arterial stiffness. Hypertension 2015;66(3):698-722, https://doi.org/10.1161/HYP.0000000000000033.
33. National Center for Health Statistics C for DC and P. *NHANES* 2015-2016 body composition procedures manual. Atlanta; 2016. https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_Body_Composition_Procedures_Manual.pdf.
34. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. U S Armed Forces Med J 1959;10(6):675-88, http://www.ncbi.nlm.nih.gov/pubmed/13659732. Accessed August 28, 2018.
35. American College of Sports Medicine. American College of Sports Medicine's guidelines for exercise testing and prescription, tenth edition. Vol 4. 10th ed. (Riebe D, ed.). Philadeplphia, PA: Wolters Kluwer Health; 2018. doi: https://doi.org/10.1046/j.1523-5408.2001.00105.x.
36. Baechle TR, Earle RW. *Essentials of strength training and conditioning.* Champaign, IL: Human Kinetics. 2008.
37. Lee DC, Schroeder EC. Resistance training improves cardiovascular health in postmenopausal women. Menopause 2016;23(11):1162-4, https://doi.org/10.1097/GME.0000000000000758.
38. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015-2020 Dietary guidelines for Americans. 8th edition. December 2015. Available at, https://health.gov/dietaryguidelines/2015/guidelines/.
39. Automated Self-Administered 24-Hour (ASA24®) dietary assessment tool. https://epi.grants.cancer.gov/asa24/. Accessed August 28, 2018.
40. Morss GM, Jordan AN, Skinner JS, et al. Dose response to exercise in women aged 45-75 yr (DREW): design and rationale. Med Sci Sports Exerc 2004;36(2):336-44, https://doi.org/10.1249/01.MSS.0000113738.06267.E5.
41. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017;70(1):1-25, https://doi.org/10.1016/j.jacc.2017.04.052.
42. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee scientific report. Washington, DC: U.S. Department of Health and Human Services, 2018.