


**REVIEW ARTICLE**

# Remotely Supervised Weight Loss and Exercise Training to Improve Rheumatoid Arthritis Cardiovascular Risk: Rationale and Design of the Supervised Weight Loss Plus Exercise Training-Rheumatoid Arthritis Trial

Brian J. Andonian,<sup>1</sup>  Leanna M. Ross,<sup>1</sup> Alyssa M. Zidek,<sup>1</sup> Liezl B. Fos,<sup>1</sup> Lucy W. Piner,<sup>1</sup> Johanna L. Johnson,<sup>1</sup> Kelsey B. Belski,<sup>1</sup> Julie D. Counts,<sup>1</sup> Carl F. Pieper,<sup>1</sup> Ilene C. Siegler,<sup>1</sup> Connie W. Bales,<sup>2</sup> Kathryn N. Porter Starr,<sup>2</sup> William E. Kraus,<sup>1</sup> and Kim M. Huffman<sup>1</sup>

Patients with rheumatoid arthritis (RA) remain at an increased risk for cardiovascular disease (CVD) and mortality. RA CVD results from a combination of traditional risk factors and RA-related systemic inflammation. One hypothetical means of improving overall RA CVD risk is through reduction of excess body weight and increased physical activity. Together, weight loss and physical activity can improve traditional cardiometabolic health through fat mass loss, while also improving skeletal muscle health. Additionally, disease-related CVD risk may improve as both fat mass loss and exercise reduce systemic inflammation. To explore this hypothesis, 26 older persons with RA and overweight/obesity will be randomized to 16 weeks of a usual care control arm or to a remotely Supervised Weight Loss Plus Exercise Training (SWET) program. A caloric restriction diet (targeting 7% weight loss) will occur via a dietitian-led intervention, with weekly weigh-ins and group support sessions. Exercise training will consist of both aerobic training (150 minutes/week moderate-to-vigorous exercise) and resistance training (twice weekly). The SWET remote program will be delivered via a combination of video conference, the study YouTube channel, and study mobile applications. The primary cardiometabolic outcome is the metabolic syndrome Z score, calculated from blood pressure, waist circumference, high-density lipoprotein cholesterol, triglycerides, and glucose. RA-specific CVD risk will be assessed with measures of systemic inflammation, disease activity, patient-reported outcomes, and immune cell function. The SWET-RA trial will be the first to assess whether a remotely supervised, combined lifestyle intervention improves cardiometabolic health in an at-risk population of older individuals with RA and overweight/obesity.

## INTRODUCTION

Despite recent, revolutionary improvements in pharmacologic management (1), rheumatoid arthritis (RA) remains associated with increased rates of cardiovascular disease (CVD) and mortality (2–5). CVD risk in RA is greatly increased compared with the general population and is at least comparable with that of

diabetes mellitus–associated CVD risk (6). CVD risk ensues early in the RA disease course (ie, within 3 to 5 years), and compared with those without RA, patients with RA have over double the risk of CVD hospitalization (4,7,8). Most importantly, CVD is the leading cause of death and reduced life expectancy in RA (9–11).

Current paradigms for the prevention and management of CVD in individuals with RA attempt to address both traditional

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<sup>1</sup>Brian J. Andonian, MD, MHSc, Leanna M. Ross, PhD, Alyssa M. Zidek, MS, Liezl B. Fos, MS, Lucy W. Piner, MS, Johanna L. Johnson, MS, Kelsey B. Belski, MS, Julie D. Counts, MS, RD, Carl F. Pieper, DrPH, Ilene C. Siegler, PhD, MPH,

William E. Kraus, MD, Kim M. Huffman, MD, PhD: Duke University School of Medicine, Durham, North Carolina; <sup>2</sup>Connie W. Bales, PhD, RD, Kathryn N. Porter Starr, PhD, RD: Duke University School of Medicine and Geriatric Research, Education, and Clinical Center, Durham VA Medical Center, Durham, North Carolina.

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Address correspondence via email to Brian J. Andonian, MD, MHSc, at [brian.andonian@duke.edu](mailto:brian.andonian@duke.edu).

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and inflammatory factors (12,13). Approximately 50% of RA CVD risk can be explained by the following traditional risks: smoking, hypertension, dyslipidemia, impaired glucose handling, and overweight/obesity (14,15). Although management of these traditional CVD risk factors is important (16), it is notable that traditional CVD risk calculators greatly underestimate RA CVD risk (17,18). Thus, recent focus in the management of RA CVD risk has been on disease-modifying antirheumatic drug (DMARD) therapy to target inflammation (16,19,20). However, the primary drawbacks to using currently available DMARD therapy to improve RA CVD risk are the same for using these powerful anti-inflammatory therapies to manage RA disease activity: immune suppression and infection risk (21). Further, the persistence and progression of CVD in RA—despite biologic DMARD agents and early intensive treatment—implies pharmacologic control of disease activity is insufficient for completely rectifying systemic consequences (10,11,22–24).

One promising means of improving RA CVD risk—for both traditional and inflammatory factors—is through overweight/obesity reduction and increased physical activity. Both overweight/obesity and physical inactivity worsen RA CVD risk, yet interventions targeting these factors to improve RA CVD risk are lacking (25–33). Here, we outline the rationale for incorporating both overweight/obesity reduction and physical activity as primary intervention strategies for RA CVD. We then discuss the potential benefits of a remotely supervised weight loss and exercise training intervention to improve use of lifestyle management strategies in RA clinical care.

## THE EFFECT OF WEIGHT LOSS ON RA CVD RISK

In the context of RA, overweight/obesity has multiple negative consequences. Overweight/obesity (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup>) is a risk factor for RA development and associates with greater disease activity, poorer treatment responses, and greater insulin resistance (25–27,34–36). Conversely, when measured by body mass index, overweight/obesity is associated with reduced RA CVD mortality rates compared with patients with RA with normal BMI (37). Although counterintuitive, this apparent reduction in CVD risk (ie, obesity paradox) appears to be a misreport driven by an underestimation of adiposity in patients with RA with normal BMI and low muscle mass (29). Indeed, obesity/adiposity is not protective of RA CVD; rather, there is a relatively greater risk for RA CVD due to loss of skeletal muscle mass (ie, rheumatoid cachexia) driven by inflammatory disease activity and physical disability (38–41).

Although unintentional weight loss leads to negative outcomes in RA, intentional weight loss provides benefits. Retrospective analyses of a cohort with RA and overweight/obesity showed weight loss of greater than 5 kg is associated with a threefold odds of improved disease activity (42). Weight loss via bariatric surgery in RA improves disease activity, medication use, and inflammatory markers, with effects sustained over 5 years

(43). One randomized controlled trial and other observational studies have shown promise in weight loss via caloric restriction for improving RA immune function and disease activity (44–47). Previous RA dietary interventions have altered macronutrient and micronutrient quality (eg, vegetarian and Mediterranean diets); however, no intervention trial has specifically assessed the effects of weight loss via caloric restriction on RA CVD risk (48,49).

## THE EFFECT OF EXERCISE TRAINING ON RA CVD RISK

In addition to overweight/obesity-related threats, physical inactivity also has negative health consequences for those with RA. Patients with RA have a very low aerobic capacity and are typically physically inactive; only 10% of patients engage in more than 30 minutes of moderate-intensity aerobic exercise per day (50,51). Physical inactivity associates with an increased risk of RA and more severe disease presentation (52,53). Physical inactivity in RA is also linked to alterations in skeletal muscle—a central component of cardiometabolic health (54). Critically important, physical inactivity intensifies the CVD risk conferred by RA (30,32,55).

Although exercise prescription for RA was traditionally controversial because of fear that excessive exercise would worsen joint disease, more recent research has shown instead that exercise training for RA is overall safe and confers many health benefits (56–58). Exercise training programs impact traditional CVD risk factors by improving RA aerobic fitness, blood pressure, lipid profiles, and body composition (ie, increased muscle mass, decreased fat mass) (59–63). Exercise training also improves RA inflammatory CVD risk factors. Both traditional aerobic/cardio training and resistance/strength training individually improve RA disease activity and systemic inflammation (64–67). Moreover, combined aerobic and resistance exercise training programs may potentially improve RA disease activity to a greater extent than either modality alone (59,63,68). Our previous work also shows that high-intensity interval exercise training improves RA disease activity, markers of inflammation (ie, erythrocyte sedimentation rate [ESR]), as well as neutrophil migration and monocyte phagocytosis (60). Despite the known benefits of exercise training for RA, the optimal dose and prescription to improve RA CVD risk remains uncertain (69).

## THE COMBINED EFFECT OF DIET AND EXERCISE TRAINING IN RA AND non-RA POPULATIONS

In persons without RA, the combination of weight loss with exercise training has greater benefit in improving CVD risk when compared with either intervention alone. This combined benefit was particularly shown in the Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE) studies, a series of randomized controlled trials of exercise training with

and without weight loss in persons at-risk for CVD but without RA (70–72). These studies show that relative to a control group that demonstrated little change in cardiometabolic risk—as measured by the continuous metabolic syndrome Z score (MSSc)—aerobic exercise training improves MSSc by  $-0.8$  (SD = 2.2). The addition of resistance exercise training incrementally improves MSSc by  $-1.1$  (SD = 1.7). Notably, adding weight loss further improves MSSc by  $-2.5$  (SD = 2.1). In a different study of older adults with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) and without RA, one year of combined weight loss and exercise training significantly reduced the prevalence of cardiometabolic syndrome and improved insulin sensitivity compared with the independent effect of either intervention (73).

Although in the general population it is clear that weight loss and physical activity have proven benefits for CVD risk and systemic inflammation, evidence of their impact on RA is currently lacking. In a randomized controlled trial comparing the health benefits of a Mediterranean diet, dynamic exercise program, or a combined diet and exercise program for women with RA, the combined program improved quality of life and disability but did not increase hand grip strength or decrease weight when compared with the individual programs (74,75). In a secondary analysis, both Mediterranean diet and dynamic exercise groups similarly decreased concentrations of serum pro-inflammatory cytokines (tumor necrosis factor  $\alpha$  and interleukin 6); the effect of the combined program on systemic cytokines was not reported (76). Altogether, given unique immune system alterations and escalating rates of overweight/obesity, physical inactivity, and CVD in RA, there is ongoing need for RA-specific trials to study the effects of combined lifestyle interventions on cardiometabolic health.

## LIFESTYLE INTERVENTIONS FOR OLDER ADULTS WITH RA

Few studies have reported the effects of lifestyle (eg, diet and exercise) interventions on clinical outcomes specifically in older adults with RA. In a randomized controlled trial of older adults (ages 65–75 years) with RA, a 20-week patient-centered supervised combined exercise (resistance and aerobic) training intervention significantly improved physical fitness, fatigue, and

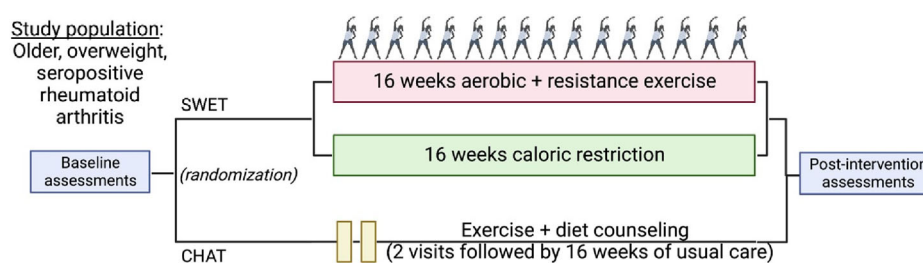
symptoms of depression and protected against increased disease activity and pain at four-year follow-up (77–79). Further knowledge of the effects of lifestyle interventions designed for older adults with RA will improve care for this patient demographic at high risk for CVD (80).

The optimal exercise dose to improve CVD in older adults with RA is unknown. Current European League Against Rheumatism guidelines for physical activity include recommendations for older patients with RA; however, these recommendations are based primarily on public health guidelines and evidence from non-RA populations (81). Public health guidelines for physical activity recommend older adults participate in multicomponent physical activity that includes balance training, aerobic training (150 minutes/week at moderate intensity or 75 minutes/week at vigorous intensity), and resistance training (2 or more days/week) (82). An area for future research is to assess whether or not these public health recommendations apply to older patients with RA.

Remote delivery of a multicomponent lifestyle intervention for older adults with RA has yet to be studied. In non-RA populations, remote behavioral intervention programs require less cost, time, and resources and are easier to implement into clinical practice compared with in-person supervised exercise—benefits that have been magnified during the COVID-19 pandemic (83,84). Importantly, remotely delivered exercise training programs associate with similar benefits—in terms of physical performance and cardiometabolic parameters—when compared with in-person programs (85). Thus, in the Supervised Weight Loss Plus Exercise Training (SWET)-RA randomized controlled trial, we will study the effects of a remotely delivered and supervised multicomponent lifestyle intervention (caloric restriction diet and exercise training based on public health recommendations) on CVD risk in older adults with RA and overweight/obesity.

## SWET-RA TRIAL DESIGN

**Overview.** The objective of the SWET-RA randomized controlled trial is to determine the effects of a 16-week remotely delivered weight loss and exercise training intervention on traditional and inflammatory RA CVD risk factors, disease activity, and patient-reported outcomes in older persons with RA and overweight/obesity. In this study, patients with RA will be randomized



**Figure 1.** SWET-RA trial design overview. CHAT, counseling health as treatment; SWET, Supervised Weight Loss Plus Exercise Training.

to one of two groups: 1) SWET or 2) counseling health as treatment (CHAT), designed to reflect current standard of care (Figure 1).

The premise of the SWET-RA trial is that 1) in RA, both overweight/obesity and physical inactivity contribute to worse disease activity (30,32,55,86–92); 2) RA CVD risk is associated with traditional CVD risk, consequences of overweight/obesity and physical inactivity, as well as disease activity and inflammation; 3) in non-RA populations, physical activity improves immune cell health (93–96); 4) in our pilot RA investigation, aerobic interval-based exercise training improved blood pressure, global health, disease activity, and reprogrammed monocyte/macrophage function (97); and 5) these improvements should be enhanced with the addition of resistance training and weight loss.

**Study population.** The study population will include adults 60 to 80 years of age with overweight/obesity (BMI 28–40 kg/m<sup>2</sup>) and seropositive (or erosive) RA, not currently meeting the 2018 Physical Activity Guidelines for Americans (82) and without absolute contraindications to exercise. For the lower end overweight/obesity BMI cutoff, we chose 28 kg/m<sup>2</sup> rather than 25 kg/m<sup>2</sup> in light of theoretical adverse effects of weight loss reducing muscle mass loss (ie, sarcopenia) in older participants with RA at lower BMI (98). Detailed eligibility criteria are shown in Table 1. Patients will be recruited from outpatient rheumatology clinics serving Duke Health in Durham, NC. Participant recruitment and study program flow are illustrated in Figure 2.

**Randomization.** Following informed consent, examination by the study physician (Table 2), and baseline assessments, participants will be randomly allocated in a 1:1 ratio blocked by age decile with a variable block size known only to the statistician. Participants and the interventionists leading the exercise and nutrition sessions will not be blinded to randomization group. The trial is single blinded with respect to the study physician performing the 28-joint disease activity examination.

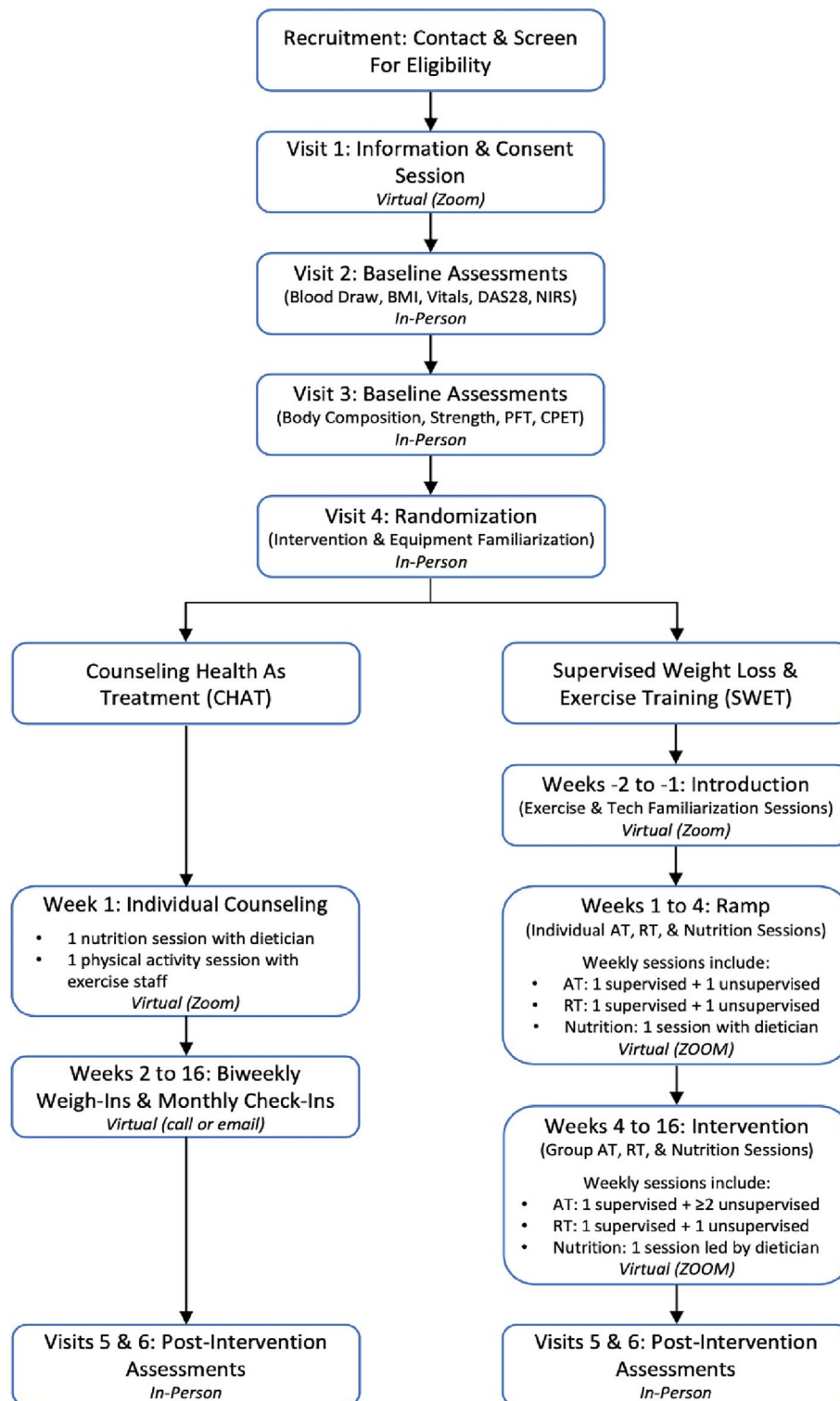
**Equipment.** Regardless of intervention group, all participants will receive the following equipment: 1) a commercial activity monitor (Garmin Forerunner 45)—study staff have access to participant physical activity data via an online platform in order to monitor intervention compliance; 2) a set of exercise resistance bands (Bodylastics Max Tension System) containing five bands with varying levels of resistance—study staff provide guidance on proper technique and use of the bands; 3) a wireless, Bluetooth-enabled digital scale (A&D Medical PLUSCONNECT wireless weight scale)—study staff monitor body weight throughout the study via the Pattern Health application (app); and 4) a tablet (Dragon Touch Notepad K10 tablet) to allow participants to use the required mobile apps.

**Table 1.** Detailed eligibility criteria for the SWET-RA trial

Inclusion criteria
Age 60–80 y
Internet access
Body mass index 28–40 kg/m <sup>2</sup>
Seropositive (positive rheumatoid factor or anticitrullinated protein antibody) or erosions typical of rheumatoid arthritis on radiographs
Exclusion criteria
Subject unwilling/unable to use online platforms (eg, ZOOM, REDCap, Pattern Health) for study activities
Current use of biologic agents other than those targeting tumor necrosis factor $\alpha$
Current (within the last month) pharmacologic therapy with corticosteroids at doses greater than prednisone 5 mg/d (or equivalent glucocorticoid doses)
Other inflammatory arthropathy or myopathy, Paget disease, pigmented villonodular synovitis, joint infection, ochronosis, neuropathic arthropathy, osteochondromatosis, acromegaly, hemochromatosis, or Wilson disease
Participating in regular exercise within the past 3 mo (according to 2018 Physical Activity Guidelines for Americans: not more than 150 min/wk of moderate-intensity exercise or 75 min/wk of vigorous-intensity exercise)
New medications within the last 3 mo
Medication-dose fluctuation within the last 30 d
Occurrence of coronary events consisting of occlusive disease (per cardiac catheterization or ST-elevation myocardial infarction), acute heart failure, or documented dysrhythmia within the last 12 mo
Current presence of aortic stenosis rated moderate or worse
Diagnosis of type 2 diabetes mellitus
Absolute contraindications to exercise: Recent (<6 mo) acute cardiac event, unstable angina, uncontrolled dysrhythmias causing symptoms or hemodynamic compromise, symptomatic aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus, acute myocarditis or pericarditis, suspected or known dissecting aneurysm, or acute systemic infection
Relative contraindications to exercise: Left main coronary stenosis, moderate stenotic valvular heart disease, outflow tract obstruction, high degree AV block, ventricular aneurysm, uncontrolled metabolic disease (eg, diabetes, thyrotoxicosis, myxedema), uncontrolled pulmonary disease (eg, severe COPD or pulmonary fibrosis), and mental (including severe depression or anxiety) or physical impairment leading to inability to exercise adequately
Significant weight change (gain or loss of >10 lb in 1 mo) within the past 6 mo
Unwillingness or inability to adhere to the diet structure of the study

Abbreviations: AV, Atrioventricular; COPD, chronic obstructive pulmonary disease; ST, segment; SWET-RA, Supervised Weight Loss Plus Exercise Training-rheumatoid arthritis.

**Remote intervention.** The SWET-RA trial uses a remotely delivered program for the implementation of a lifestyle intervention for patients with RA. Aside from preintervention and postintervention assessment visits and program introduction visits (Figure 2), all intervention delivery and application are completed via video conference (ie, Zoom), the study YouTube channel, and the study mobile



**Figure 2.** SWET-RA trial participant recruitment and study program flow diagram. AT, aerobic training; BMI, body mass index; CPET, cardiopulmonary exercise testing; DAS28, disease activity score in 28 joints; NIRS, near-infrared spectroscopy muscle oxidative capacity testing; PFT, pulmonary function testing; RT, resistance training.

apps (Pattern Health: <https://pattern.health>; MyFitnessPal: <https://www.myfitnesspal.com>) (Figure 3). The study mobile apps connect to and obtain data from study equipment (eg, heart rate and step

counts from activity monitor, weight from digital scale). Via the study mobile apps on the provided tablet, study participants 1) view all individualized intervention related information, 2) record completion



**Table 2.** Physician screening assessment for the SWET-RA trial

Study physician screening assessment
Functional capacity assessment “What limits you when you exercise or exert yourself? Breathing, fatigue, pain?” Observation, physical examination
Cardiorespiratory fitness assessment “How far are you able to walk/run/bike/swim?” Observation, physical examination
Muscle strength assessment “How much are you able to lift/carry?” Observation, physical examination
Dynamic balance/flexibility assessment “What kind of activities do you feel comfortable performing?” Observation, physical examination

Abbreviation: SWET-RA, Supervised Weight Loss Plus Exercise Training-rheumatoid arthritis.

of intervention goals, and 3) receive feedback and reminder notifications regarding weekly task completion.

**SWET intervention.** Participants randomized to the SWET group will complete three supervised components: weight loss, aerobic training, and resistance training.

*Weight loss component.* Following a randomization and a virtual equipment familiarization session, participants will meet

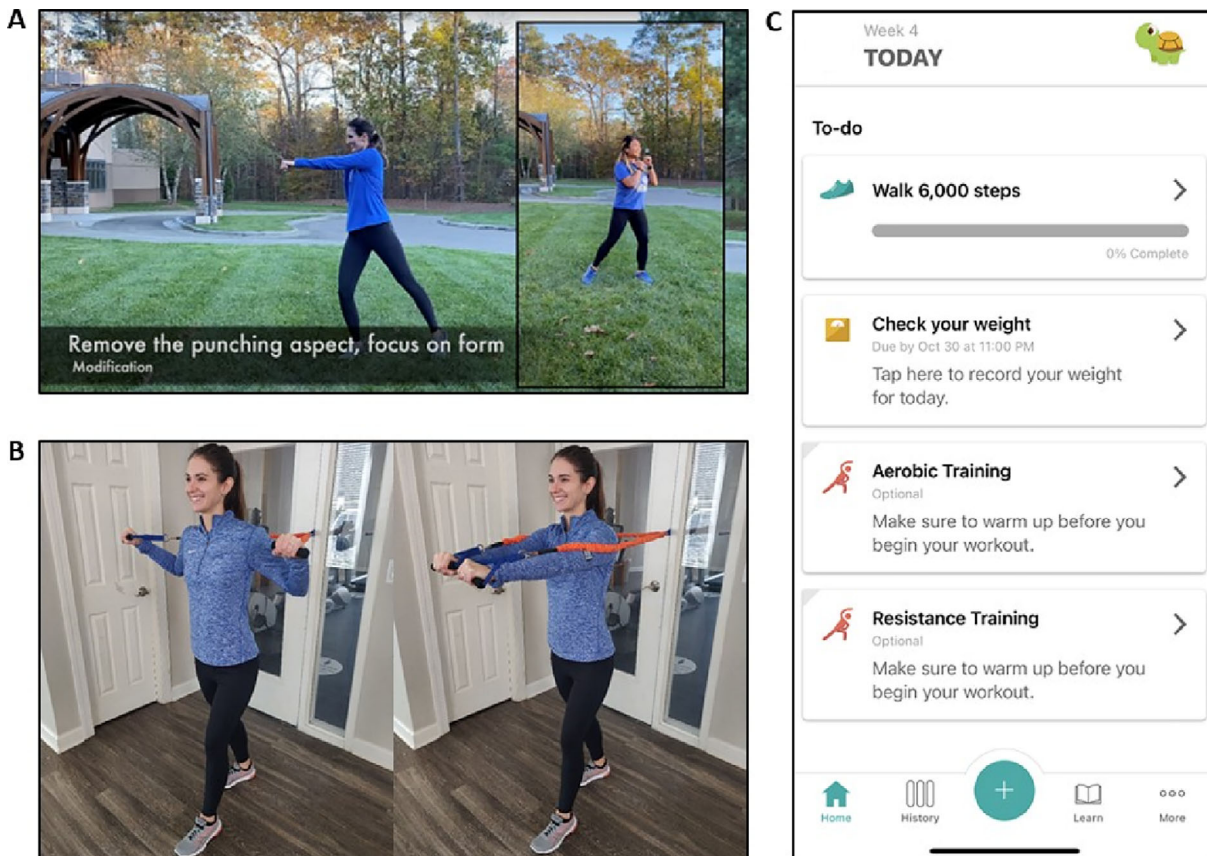
(virtually, in real time) with a registered dietitian to receive an individualized caloric restriction diet prescription. Prescriptions are calculated as below using participant data and estimated total energy expenditure (TEE) (99):

$$TEE \text{ for men with obesity: } 864 - (9.72 \times \text{Age [y]}) + \text{Physical Activity Level} \times (14.2 \times \text{Weight [kg]} + 503 \times \text{Height [m]}).$$

$$TEE \text{ for women with obesity: } 387 - (7.31 \times \text{Age[y]}) + \text{Physical Activity Level} \times (10.9 \times \text{Weight[kg]} + 660.7 \times \text{Height[m]}).$$

The prescribed calorie amount for a weight loss of approximately 1 to 2 pounds (average of 0.6 kg) per week is based on a reduction of 500 to 1000 kcal/day below TEE; the 16-week target is 7% weight loss with an expected achievement of 5%. The macronutrient distribution of the SWET diet is 40% carbohydrate, 30% fat, and 30% protein.

Each week, participants will attend one live, virtual group nutrition session led by a registered dietitian. The nutrition curriculum is designed to enhance diet compliance, including group support, goal setting, self-monitoring, stress management, problem solving, relapse prevention, daily diet journaling, email/phone reminders, and tutorials for online tools. To reduce the difficulty with imposing two behavioral changes simultaneously (ie, diet



**Figure 3.** SWET-RA remote lifestyle intervention. **A,** Screenshot example of aerobic training video. **B,** Screenshot example of resistance training video. **C,** Screenshot of mobile app (Pattern Health). SWET, SWET, Supervised Weight Loss Plus Exercise Training.

and exercise training), the curriculum is individualized with focus on use of dietary exchanges and understanding of the diet prescription during the initial weeks with progression toward more complex topics and more aggressive weight loss goals. Diet compliance is monitored by weekly weigh-ins and weekly collection of daily food records captured via the A&D scale and the study mobile apps, respectively. Additionally, participants will use a weight loss graph to track their weight loss throughout the 16 weeks. As a part of baseline and postintervention assessment visits, participant 3-day food diaries will be collected to determine diet intake (calories, macronutrients, and micronutrients) using Food Processor Nutrition Analysis Software (version 11.0.3, ESHA Research, Salem, OR).

**Aerobic exercise training component.** The remotely supervised aerobic exercise component is based on US physical activity guidelines (82) and consists of two weekly goals: 150 minutes of moderate-to-vigorous exercise and an average of at least 6000 steps per day. Because moderate- to vigorous-intensity exercise varies according to fitness level, participants will receive individualized prescriptions based on results from a cardiopulmonary exercise test with gas exchange. Exercise intensity is prescribed as the participant's heart rate range that corresponds to moderate-to-vigorous intensity (ie, 45%-65%  $\text{VO}_2$  reserve), calculated as 45% to 65% of the participant's heart rate reserve (ie, maximum minus resting heart rate).

Participants will undergo an initial ramp period in which study staff exercise physiologists virtually counsel participants on understanding device use, heart rate ranges, and exercise safety while exercises are performed at lower intensities. Over 1 to 2 weeks, intensities progressively increase.

Each participant's exercise prescription will include required attendance at a live, remotely supervised online aerobics class once per week. Conducted via Zoom, an exercise physiologist conducts a 45- to 60-minute class, comprising a warm-up, one to four sets of moderate aerobic activities that can be done without equipment, and a cool down. During these sessions, participants will monitor heart rates with their Garmin devices (with staff assistance, as needed) to modify activities to maintain heart rates within the prescribed range. Participants will also report an overall rating of perceived exertion (RPE) for each training session (Borg scale 6-20). Aerobic exercises are individualized by study staff exercise physiologists and physicians to ensure pain-free range of motion (eg, adapting movements for individuals with chronic joint deformities related to RA).

In addition to the live virtual exercise class, participants will be instructed to perform aerobic exercises on their own to meet both their step count and aerobic minutes goals. Aerobic exercises include (but are not limited to) aerobics videos (recorded on study YouTube channel by study staff exercise physiologists), walking, running, and dancing; diversity of aerobic exercise modalities was chosen to accommodate patient preference and increase exercise prescription compliance.

**Resistance exercise training component.** Remotely supervised resistance training exercises will be primarily performed with resistance bands; resistance bands were the chosen modality because of practicality (ie, ease of use at home), low cost, similar strength benefits compared with conventional resistance training devices (eg, weight machines and dumbbells), and functional benefits for patients with arthritis (eg, resistance does not rely on gravity, less stress on hand/wrist joints compared with conventional devices) (100). The resistance training goal includes twice weekly sessions, on nonconsecutive days. Resistance training sessions consist of 10 to 11 exercises targeting major muscle groups (1-3 sets of 8-15 repetitions with a rest period of at least 60 seconds between sets). A virtual equipment familiarization session with an exercise physiologist will introduce participants to the exercise bands, targeted muscle groups, and proper technique. After a warm-up period, the exercise physiologist and the participant will work together to decide on a comfortable resistance band (ie, resistance level) to use for each of the 10 to 11 exercises to determine an individualized exercise prescription. The starting band resistance will be set when the participant can perform one set of 8 to 10 repetitions comfortably using proper technique.

Safe and effective resistance exercise technique will be emphasized to promote full range of motion, activation of targeted muscle groups, and proper breathing. Over the 16-week intervention, the amount of resistance lifted and/or repetitions or sets performed will be slowly increased such that progression occurs while minimizing musculoskeletal injuries. After two back-to-back training sessions during which 3 sets of 15 repetitions are performed with proper technique, resistance will be increased (typically by 5%-10% or one band resistance level) such that 1 to 3 sets of 8 to 10 (but not 15) repetitions can be performed using proper technique. Similar to aerobic exercise modifications, resistance exercises are individualized by study staff exercise physiologists and physicians to ensure pain-free range of motion.

As with weekly aerobic exercise sessions, participants will be required to attend one live virtual resistance exercise class (supervised by an exercise physiologist) and complete one session on their own. Recordings of both aerobic and resistance exercise routines by study staff exercise physiologists are available on the study YouTube page for participants to view at any time.

**CHAT intervention.** Participants randomized to the CHAT group will receive initial clinical counseling on healthy diets and physical activity.

**Diet counseling.** Participants will meet virtually one-on-one for approximately 60 minutes with a registered dietitian for dietary recommendations to improve overall health (101). Recommendations are to 1) follow healthy eating patterns; 2) focus on variety, nutrient density, and amount; 3) limit calories from added sugars and saturated fats and reduce sodium intake; 4) shift to healthier food and beverage choices; and 5) support healthy eating patterns. Participants will be given written summaries of the

recommendations. In addition, participants will be asked to check their weight using the study-provided A&D scale every 2 weeks. As part of baseline and postintervention assessment visits, 3-day food diaries will be analyzed for total calories, macronutrient, and micronutrient consumption using the Food Processor software.

*Physical activity counseling.* Participants will also meet virtually one on one for approximately 60 minutes with an exercise physiologist for recommendations of physical activity to improve overall health. Aerobic activity recommendations target at least 6000 steps per day and five 30- to 35-minute aerobic exercise sessions (eg, walking) per week in accordance with public health recommendations for adults (82). Discussions include how to assess daily steps and how to increase daily steps each week until the 6000 step per day target is reached. Aerobic exercise is recommended at a moderate intensity and described as a 12 to 14 on the Borg RPE scale. Participants will be provided with written summaries of these recommendations. Resistance training recommendations are two sessions per week, each separated by at least 48 hours. Written instructions for 8 to 10 upper- and lower-body resistance exercises using resistance bands will be provided. In addition to the commercial activity monitors, participants will be provided with an exercise journal to record daily steps and exercise sessions. Each week, activity monitor data will be downloaded for computerized analysis. To minimize attention bias, study staff will contact CHAT participants once monthly through phone or email to ensure they do not have any questions or concerns.

**Outcome measures.** Assessing CVD risk in RA is controversial. Despite a general consensus that RA disease activity contributes to CVD risk, RA-specific risk calculators perform similar to calculators designed for general populations (102,103). Additionally, most calculators use presence or absence of risk factors, which (especially for type 2 diabetes or coronary artery disease) are unlikely to be reversed in a 16-week nonpharmacologic intervention; thus, patients with these conditions are excluded from the study.

The primary outcome chosen to assess change in cardiometabolic risk following the intervention period is the MSSc (70,71,104). The MSSc is a continuous weighted score of the five metabolic syndrome variables—fasting high-density lipoprotein cholesterol, triglycerides, glucose, waist circumference, and mean blood pressure. A modified Z score will be calculated for each participant using continuous differences between the Adult Treatment Panel (ATP) III guideline values and participant values with normalization to the cohort's standard deviations. To account for variations in ATP III criteria between men and women, we will use sex-specific MSSc equations (105,106). Secondary outcomes include markers of inflammatory disease activity, immune cell function, body composition, cardiorespiratory and muscle fitness, pulmonary function, and self-reported health.

*Anthropometrics and vital signs.* With the participant wearing lightweight clothing and no shoes, height and body weight will be measured with a stadiometer and digital scale, respectively. Although the participant stands with legs parallel and shoulder-width apart, waist circumference will be measured with a flexible tape measure at the minimal waist (ie, smallest horizontal circumference above the umbilicus and below the xiphoid process) (107). Resting blood pressure and heart rate will be measured after the participant has relaxed in a seated position for approximately 5 minutes.

*Body composition.* Fat mass and fat-free mass will be assessed under similar conditions of hydration among participants via air displacement plethysmography (BOD POD<sup>®</sup> Life Measurement, Concord, CA).

*Blood-based biomarkers.* Following an overnight fast, blood samples will be obtained and analyzed for fasting glucose, insulin, and lipid/lipoprotein profiles; complete blood count with differential and platelet count; ESR; and high-sensitivity C-reactive protein (CRP). In addition, peripheral blood mononuclear cells will be immediately isolated and stored frozen in liquid nitrogen for future assessment of immune cell function measures, including monocyte/macrophage function, differentiation, and phenotype distributions.

*Disease activity.* Overall RA disease activity will be assessed with the disease activity score in 28 joints—a composite measure including ESR (or CRP), a self-reported overall health assessment on a 100 mm visual analog scale, and the number of tender and swollen joints determined from a 28-joint examination by the blinded study physician (108).

*Cardiorespiratory fitness.* Under study physician supervision, cardiorespiratory fitness (ie, peak  $\text{VO}_2$ ) will be determined by graded maximal cardiopulmonary exercise tests performed with 12-lead electrocardiography and continuous expired gas analysis (TrueMax Parvomedics, Provo, UT). Blood pressure and RPE (Borg scale 6-20) will be monitored throughout the test. The graded treadmill protocol consists of 2-minute stages and begins at 1 mph and 0% grade, then increases speed and/or grade until the subject reaches volitional exhaustion (109).

*Muscle fitness.* Muscle strength assessments include tests of quadriceps strength via isometric knee extension (CYBEX, Stoughton, MA) and bilateral grip strength (hand-held dynamometer). Forearm (flexor digitorum profundus) and calf (medial gastrocnemius) muscle oxidative capacities will be estimated using near-infrared spectroscopy, which measures oxygen consumption ( $m\text{VO}_2$  as the recovery rate constant  $k$ ) recovery kinetics and intramuscular oxyhemoglobin and deoxyhemoglobin concentrations following a sequence of brief, rapid arterial cuff occlusions (110).

*Pulmonary function.* Pulmonary function will be assessed by spirometry (TrueMax Parvomedics).

*Questionnaires.* Medical history, current medication use, and demographics will be assessed at baseline. Baseline and postintervention self-reported measures of global health, pain, fatigue, physical function, sleep, and self-efficacy for managing disease



are derived from the Patient-Reported Outcomes Measurement Information System (PROMIS) bank (<https://commonfund.nih.gov/promis/index>).

**Sample size.** Sample size calculations are based on data from the STRRIDE studies. We expect MSSc improvements to be comparable to those observed for aerobic training and weight loss in the SWET that includes aerobic training, weight loss, and resistance training. Thus, to detect a STRRIDE-like significant difference between SWET and the CHAT of  $-2.5$ , assuming a SD for change of  $2.1$ , 20 persons total (10 per group) will deliver 82% power at a one-tailed  $\alpha$  of  $0.05$  and group difference of  $2.33$ . We chose a one-tailed test because a result in the opposite direction (i.e., metabolic syndrome score reduction in CHAT exceeding SWET) would not change clinical practice (111). Based on our prior experience, we expect an attrition rate of 20% to 25% during the intervention period. Thus, 26 participants with RA will be enrolled and randomized.

**Statistical analysis plan.** For study analyses, the key questions are what is the impact of the intervention on primary and secondary outcomes? The primary outcome, MSSc, will be measured at two timepoints, preintervention (ie, week 0) and postintervention (ie, week 16). To analyze, we will use regression and calculate change (post-pre). Thus, at a simple level our model is  $\Delta\text{MSSc}_i = \beta_0 + \beta_1\text{baselineMSSc}_i + \beta_2\text{SWETGroup} + \epsilon_i$ , where  $\beta_2$  is the group effect for the primary outcome. We will control for baseline MSSc (112) to assess group differences while controlling for between-group differences at baseline. Other important covariates measured at baseline can be incorporated into the model. All enrolled participants will be analyzed in an intention-to-treat fashion. Statistical significance will be established as  $P < 0.05$  for the primary outcome, MSSc. Secondary outcomes will be assessed similarly, yet without control for type I error.

## CONCLUSIONS

The SWET-RA trial will be the first randomized controlled trial to assess the effects of a remotely delivered weight loss and exercise training lifestyle intervention on health parameters in patients with RA. The primary outcome is change in CVD risk in older patients with RA and overweight/obesity who are at high risk for cardiometabolic disease. The SWET arm of the study will pioneer a remotely delivered, behavioral intervention as a means to implement lifestyle medicine to larger groups of patients with rheumatic disease. The scalability of the SWET intervention and platform will need to be further assessed in future larger studies. Identification of the effects of exercise plus weight loss in persons with RA on CVD risk, disease activity, as well as self-reported outcomes, will have broad implications for clinical practice and patient uptake of clinician recommendations.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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