Trials

STUDY PROTOCOL

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Protocol for a randomized controlled trial of a resistance exercise training to treat major depression via cerebrovascular mechanisms (RESIST Trial)

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Abstract

Background Many adults with major depressive disorder (MDD) do not engage in treatment and may also not respond when current frontline treatments are completed. Resistance exercise training (RET) is an understudied behavioral treatment option, which may help with MDD management through improving cerebral blood flow that is commonly impaired in adults with MDD. The purpose of this study is to use gold-standard research methods to determine the validity (clinical efficacy) of RET for treating MDD and to determine potential cerebrovascular pathways through which RET might improve MDD symptoms.

Methods This study will be a randomized controlled trial of 200 adults with DSM-5-diagnosed MDD of at least mild severity. Participants will be randomized to 16 weeks of twice-weekly RET at either guidelines-based high dose (60% one-repetition maximum initial load; $n=100$) or a low-dose/SHAM (30% one-repetition maximum initial load; $n=100$) progressive, upper- and lower-body program using resistance machines. The primary clinical outcomes of this trial are depressive symptom severity, assessed via clinician-rated GRID-Hamilton Depression Rating Scale and self-reported Quick Inventory of Depressive Symptomatology. Secondary outcomes that will examine potential mediators are cerebral blood flow (via cerebral blood velocity and pulsatility) and self-efficacy (via New General Self-Efficacy Scale and RET Task Self-Efficacy). Group differences will be evaluated during assessment visits at weeks 0 (Baseline), 8, 16 (Post-Intervention), 26, and 52. Additional analyses will explore predictors of treatment success and participants' maintenance of the RET past the active intervention.

Discussion RET is an understudied behavioral treatment for MDD. This randomized controlled trial will critically build on previous studies by using a large sample size, rigorously examining potential (provocative, plausible) biological and psychological mechanisms of RET's hypothesized antidepressant effects, and determining potential persistent effects with short- and long-term follow-up assessments. If clinical efficacy is confirmed, RET would be added as a highly translatable, accessible, low-cost alternative treatment option for individuals with MDD. Further effectiveness and implementation research would be required if efficacy is confirmed in this trial.

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Trial registration This trial is registered on ClinicaTrials.gov (ID: NCT06110897; October 20th, 2023; https://clinicaltrials.gov/study/NCT06110897).

Keywords Resistance exercise training, Strength training, Major depressive episode, Cerebral blood flow, Antidepressant mechanism, Efficacy, Precision medicine, Sham comparator

Administrative information

Note: The numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	**Protocol for a randomized controlled trial of a resistance exercise training to treat major depression via cerebrovascular mechanisms (RESIST Trial)**
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Introduction

Background and rationale {6a}

Depression is highly prevalent, and adults with major depressive disorder (MDD) have one or more major depressive episodes in their lifetime [34]. The cyclical nature of MDD, along with pandemic-associated increases in negative mood symptoms [22], will increase the prevalence rate now and into the future. Unfortunately, the success rate of standard care is low at only 29% at 1 year [99]. Antidepressant medications are the most common treatment, although antidepressant prescription suffers from high attrition and frequent poor outcomes [45, 53], with many patients preferring non-pharmacological treatments [12, 32]. Considering (1) high and increasing rates of MDD, (2) patient desire for non-pharmacological treatment [32, 47, 61], and (3)

poor long-term treatment effectiveness [99], there is a critical need to develop scalable non-pharmacological treatments for adults with MDD to increase short- and long-term treatment success.

Resistance Exercise Training (RET) is a potentially promising non-pharmacological treatment option for MDD that is understudied. While aerobic exercise training (e.g., continuous-intensity cardiorespiratory exercise) has been found to be similarly effective to pharmacotherapy [9, 10] and psychotherapy [16, 30, 60] for treating MDD, substantially less is known about the benefits of RET for MDD. A meta-analysis on the efficacy of RET for reducing depressive symptoms demonstrated the potential benefits of RET overall ($d=0.66$) and specifically for samples with symptoms indicative of mild-to-moderate depression at baseline ($d=0.90$), though only four studies included samples with clinical depression [29]. Progressive RET (i.e., RET with progressive increases in load) has the potential to provide greater antidepressant effects than aerobic exercise or other treatments for many reasons, including specific targeting of cerebrovascular mechanisms that may underlie depression [92], consistent increases in workload leading to self-confidence increases [36, 89], or, plausibly, consistent and regular mood state improvement from each set or session. Further, RET's ability to also lower the risk of frequent depression comorbidities, such as early mortality, hypertension, neurodegeneration, and diabetes, makes it a potentially ideal intervention for the overall health of adults with MDD [54, 54, 55, 55, 83, 87]. Therefore, RET's known antidepressant and cardioprotective effects in non-MDD populations make it a promising treatment option that may simultaneously treat MDD and its major comorbidities.

The extant intervention literature suggests that RET has the potential to produce large antidepressant effects, but the underlying mechanisms are unclear and understudied. Cerebral blood flow has emerged as a candidate mechanism in MDD [1]. Individuals with MDD exhibit altered cerebral blood flow [8, 35, 52, 97, 98] and impaired cerebral pulsatility (a measure of how flow fluctuates within a cardiac cycle [50, 70, 73, 104]). Additionally, reduced regional blood flow is associated with incident depression [23], longer symptom duration [17], and higher symptom severity [79]. As such, cerebrovascular variables may represent promising mechanistic targets for MDD treatments. In support of this, normalization of cerebral blood flow [7, 27, 40, 59, 101] is associated with successful non-pharmacological and pharmacological MDD treatment [41]. Cerebrovascular variables are responsive to exercise training and may mechanistically contribute to successful treatment of MDD. Additionally, preliminary data suggests that RET can improve cerebrovascular targets in adults with MDD [62]. A 16-week pilot single-arm RET trial in adults with MDD found improvements in middle cerebral artery (MCA) blood velocity, conductance, and cerebral pulsatility, with the improvements moderately correlated with depressive symptoms (correlation coefficients $=-0.15$ to -0.43). Cumulatively, past work and pilot data provide preliminary evidence that cerebrovascular targets may be underlying mechanisms for the treatment of depression (particularly RET) and support further research in larger sample sizes.

Finally, there is substantial interest in precision medicine or identifying the best intervention for each individual [15]. In particular, much has been done to attempt to identify optimal intervention approaches for psychiatric diagnoses [57, 86], yet current advances have been slow. It is expected that information across multiple domains (e.g., blood biomarkers, imaging, clinical characteristics, history) will be required to generate classification trees that optimize treatments on an individual basis with high accuracy and precision. Therefore, the present project will collect data across multiple levels of analysis to train machine learning algorithms to predict treatment success at the individual level. If successful, this approach has the potential to aid in predictions about (1) who would adhere to a resistance exercise prescription while also determining for whom resistance exercise would be expected to have the largest (2) antidepressant and (3) cerebrovascular effects, and the potential modifiability of these predictors.

Objectives {7}

Thus, the purpose of this trial is to (1) confirm the efficacy of RET for MDD in a fully powered efficacy trial, (2) understand potentially relevant cerebrovascular mechanisms, and (3) identify modifiable and non-modifiable predictors of RET's efficacy for treating MDD. Our central hypothesis is that 16 weeks of progressive RET ("High-Dose") will reduce depressive symptoms in adults with MDD by improving MCA blood velocity and cerebral pulsatility compared to a time- and attention-matched SHAM control ("Low-Dose"). This trial builds on past work by completing a confirmatory efficacy trial of sufficient size, length, and follow-up to detect a clinically meaningful effect with mechanistic testing. As such, it has the potential to expand treatment options for adults with MDD while providing mechanistic and behavioral factors related to treatment efficacy.

Trial design {8}

This is a two-arm 1:1 randomized controlled trial comparing 16 weeks of a standard, high dose ($n=100$;

High-Dose) versus 16 weeks of a low dose/SHAM ($n=100$; Low-Dose) of resistance exercise training in adults with MDD of at least mild severity (as determined by structured clinical interview), using a superiority hypothesis framework (i.e., High-Dose > Low-Dose on change in depressive symptoms from Intake to Week 16 Assessment visit).

This trial is registered with ClinicalTrials.gov (ClinicalTrials.gov ID: NCT06110897; Protocol ID: R01MH130566; Registered on 10/20/2023). It was funded by the National Institute of Mental Health (NIMH; FAIN#: R01MH130566), titled "Resistance Exercise to Treat Major Depression via Cerebrovascular Mechanisms: Confirming Efficacy and Informing Precision Medicine." The "RESIST Trial" will be used in public facing documents. All procedures have been reviewed and approved by university institutional review boards, and all items included in the WHO Trial Registration Data Set can be found on ClinicalTrails.gov or in this publication.

Methods: participants, interventions, and outcomes

Study setting {9}

All data collection for Assessment Visits will occur in private research facilities and RET Sessions will occur in local research spaces.

Eligibility criteria {10}

Inclusion criteria for this trial include the following: (1) a diagnosis of DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) MDD, confirmed via Structured Clinical Interview for DSM-5 (SCID), (2) current depressive symptoms of at least mild severity defined by a Hamilton Rating Scale of Depression (using the GRID-HAMD) score greater than or equal to 8, (3) be ages 18–65, (4) EITHER not take any mental health medications or use other mental health treatment (e.g., behavioral, psychological) OR be on a stable mental health medication and/or treatment regimen for the past 8 weeks, and be willing to maintain that regimen for the duration of the study, (5) provide physician clearance for completing resistance exercise training prior to enrolling in the study, and (6) be willing to be randomized to either resistance training group.

Exclusion criteria include the following: (1) being currently pregnant, nursing, or planning to become pregnant during the study, (2) being diagnosed with current Substance Use Disorder via the SCID, (3) being diagnosed with lifetime or current Psychosis, Mania, or Bipolar Disorder via the SCID, (4) having class III + obesity (BMI greater than or equal to 40), (5) active suicidal ideation with specific plan and intent ('5' score on Suicidal Ideation from Columbia Suicide Severity Rating Scale [C-SSRS]), (6) currently meeting RET recommendations (2 days per week) for the last 8 weeks (i.e., is currently engaged in regular RET), (7) self-reporting recent (within 3 months) severe concussion or traumatic brain injury, (8) having cardiovascular disease, (9) having uncontrolled hypertension (> 160/100 mm Hg), (10) having uncontrolled diabetes (i.e., having diabetes without medical management), or (11) exhibiting behavioral disturbance (e.g., aggression, mild-moderate cognitive impairment) or relationships with study team members (e.g., clinical interviewers) that would significantly interfere with study participation, as assessed by research personnel.

Who will take informed consent {26a}

Individuals interested in participating will complete an online screening survey to assess basic eligibility criteria. Eligibility criteria will subsequently be verified via a phone screening survey. If potentially eligible, individuals will attend an Intake Visit, led by senior research personnel, knowledgeable about all study procedures. Informed consent will occur at the beginning of the visit, and participants will be asked to thoroughly read the informed consent document. The research team will leave the room to minimize influence and allow ample reading time. After, participants will be given a verbal overview of the document, figures showing study visit flow, and images of the exercise space and cerebrovascular assessments, allowing additional opportunities for questions. After all questions are answered, interested participants will sign the informed consent document electronically on REDCap and enroll in the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The informed consent form includes language regarding the potential use of data beyond the specific plans of this study, stating in all future analyses, only de-identified data will be shared.

Interventions

Explanation for the choice of comparators {6b}

Progressive, High-Dose RET is hypothesized to improve mechanistic targets and improve MDD, and is designed in accordance with US Physical Activity Guidelines (i.e., moderate to high intensity, twice-weekly, progressive, upper- and lower-body). Low-Dose (SHAM) was selected as the comparator because the intensity is expected to not influence mechanistic targets or lead to substantial symptom improvement (beyond non-specific placebo effects). Low-Dose participants will undergo identical procedures as High-Dose (e.g., sets/reps, session length, interaction with team), rigorously controlling for both time and attention.

Intervention description {11a}

High-Dose

Participants randomized to High-Dose will complete 16 weeks of guideline-based, progressive, whole-body RET twice per week, beginning their workload at 60% of their estimated 1RM. Each session, they will complete 3 sets of 8–12 repetitions for all machines and complete 3 sets of an abdominal exercise (i.e., planks [~15–60 s] or crunches [12 reps per set], each with or without weight, depending on fitness). The lifts performed via the machines include leg press, leg extension, leg curl, chest press, seated row, military press, lat pull down, arm curl, and arm extension. When the participant completes 12 reps on all 3 sets for two consecutive sessions, they will increase their resistance by 5% of that session's weight during their next session. The progression will occur on an exercise-by-exercise basis.

Low-Dose

Participants randomized to low-dose will complete 16 weeks of progressive, whole-body RET twice per week, but begin their workload at 30% of their estimated 1RM. Identical to High-Dose, each session, they will complete 3 sets of 8–12 repetitions for all machines and complete 3 sets of an abdominal exercise (i.e., planks [~15–60 s depending on ability] or crunches [12 reps per set with no or very little weight, depending on ability]). For progression, every four sessions (rather than two in High-Dose) that the participant completes all 3 sets with 12 reps of each exercise, either all lower or all upper body exercises will have their load increased by 5% of their previous load. An upper/lower body split will be used to enhance motivation allowing for lower body to increase after the first 2 sessions and then every four sessions thereafter (e.g., session 6/10/14/etc.), with increases in either upper or lower body possible each week, while maintaining a low overall progression throughout the entirety of the 16 weeks. If participants increase at each available opportunity, this progression will result in 7–8 load increases per machine, closely matching that which occurred during a single-arm High-Dose pilot trial [62]. As goal attainment and visible progress are motivators and reinforcers of exercise behavior, it is expected that these similar increases will reduce potential between-group variability in adherence to the intervention. Further, the intensity will not exceed 45% of the participant's initial estimated 1RM, ensuring mutually exclusive intervention groups (i.e., Low- Dose vs High-Dose will exercise at 30–45% vs 60%+of initial 1RM, respectively, across the 16 weeks).

Criteria for discontinuing or modifying allocated interventions {11b}

To ensure participant safety, participants will be required to exit the study and be connected with a higher-level of care in case of substantial safety concerns: (1) a participant is hospitalized overnight for suicidality, (2) a participant indicates high risk of suicide on the C-SSRS or Quick Inventory for Depressive Symptoms (QIDS), (3) law enforcement is called and transports the participant to emergency services, or (4) a participant attempts suicide at any point during the study.

Strategies to improve adherence to interventions {11c}

Strategies from theories of exercise behavior change, including increasing intrinsic motivation, developing exercise preparation habits, and completing commitment assessments, will be used to promote intervention adherence [75]. Participants will engage in an initial planning period, reflecting about intrinsic motivations for beginning RET sessions, developing exercise habit preparation action and coping plans directly related to their RET sessions, and confirming their level of commitment (e.g., provide signature verifying attendance of next RET Session). They will then complete weekly reflections to reassess motivation, habit development, and commitment, and to provide ongoing checks and frequent communication regarding adherence with the study team. Further, constructs related to adherence (e.g., exercise identity, intrinsic motivation, habit development, and self-efficacy) will be formally measured (e.g., Exercise Identity Scale, General Self-Efficacy Scale, Self-Reported Behavioral Automaticity Index, and items from the Behavioral Regulation of Exercise Questionnaire) during assessment visits. The combination of both process and outcome adherence measures will facilitate intervention adherence and allow for examination of predictors of adherence, both during the active intervention (adherence to RET sessions during the intervention) and afterwards (maintenance of RET participation after the 16-week intervention period) to improve future behavioral interventions for long-term management of MDD.

Relevant concomitant care permitted or prohibited during the trial {11d}

Inclusion criteria (i.e., either not engaging in any mental health treatment OR on a stable mental health treatment regimen for at least 8 weeks and willing to maintain it for the length of the intervention [washout period]) will be used to minimize any impact of concomitant care. This criterion allows enrollment of the target participants (i.e., individuals who may benefit from either beginning a new treatment or adding a supplemental treatment), while minimizing the potential confounding effects of extraneous treatment changes (e.g., beginning a new medication during the intervention). Any ongoing changes in mental health treatments during the study will

be systematically evaluated during each assessment visit, and change will be documented but will not terminate study participation.

Provisions for post-trial care {30}

During the Week 16 Assessment Visit, participants will be told they are able to engage in any additional and/or different mental health treatments. All participants will be provided with information about local mental health clinics, and the Clinical Interviewer will help connect them with the appropriate mental health services. If suicide-related items are endorsed via the C-SSRS at any time, the safety plan (created during the Intake Visit) will be reinforced and updated as needed, and the participants will be connected to local emergency services or continuing outpatient care, as needed. Additionally, participants will be provided with information regarding resistance exercise training prescriptions, their current workload, and local gym options to continue RET, if desired.

Outcomes {12}

Assessment timing across the 52-week study is detailed for primary, secondary, and tertiary outcomes in Table 1.

Primary [76]

Depressive symptom severity

Depressive symptom severity is the primary clinical outcome in this trial, assessed using the GRID-Hamilton Depression Rating Scale (GRID-HAMD; [33, 103]). It is a 17-item clinician-completed questionnaire used to rate depressive symptom severity by probing mood, feelings of guilt, suicidal ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. Scores of all 17 items are summed for a total score, and higher scores reflect greater symptom severity. GRID-HAMD scoring is categorized as Normal (0–7), Mild Depression (8–13), Moderate Depression (14–18), Severe Depression (19–22), and Very Severe Depression (>23). Comparisons between groups will be made at all assessment visits using group mean change scores from the Intake Visit, with Intake and Week 16 Assessment Visit the primary timepoints. Interviews will be conducted by Clinical Interviewers, blinded to treatment assignment, trained in the use and scoring of this instrument. Interrater reliability for the GRID-HAMD is high (ICC = 0.95) and internal reliability is acceptable ($\alpha = 0.78$; [103]).

The Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR; [82]) will be used to assess participants' self-reported depressive symptom severity. The QIDS-SR is a 16-question instrument focused on the past 7 days, with items scored on a scale from 0 to 3. The sum of nine domains (i.e., sleep disturbance, sad mood, changes in weight or appetite, concentration, self-criticism, suicidal ideation, interest, energy or fatigue, and psychomotor agitation or retardation) is used to determine the severity of depression, with scores ranging from 0 to 27. Scores are categorized as: no depression (0–5), mild depression (6–10), moderate depression (11–15), severe depression (16–20), and very severe depression (21–27). Comparisons between group averages will be evaluated weekly (i.e., RET sessions 1–16) and at each assessment visit to corroborate clinician-rated depressive symptom severity. Internal consistency for the QIDS-SR is high ($\alpha = 0.86$; [82]). Mean continuous change scores from Intake to Week 16 Assessment Visits will be the primary metric and timepoint of interest.

Clinical diagnosis of depression

The Structured Clinical Interview for DSM-5 Disorders, Researcher Version (SCID-R; [26]) will be administered to confirm MDD diagnosis, identify exclusionary diagnoses, and track changes in MDD remission rates across time. The SCID is a semi-structured interview used for making diagnoses according to the diagnostic criteria published in the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM-5, 2013). The following sections will be assessed: Mood Episodes, Psychotic and Associated Symptoms, Substance Use Disorders, and Anxiety Disorders. Other non-exclusionary diagnoses not covered in these sections will systematically be self-reported via a questionnaire verbally administered by the Clinical Interviewer. The SCID-R will be administered at each assessment visit by a trained interviewer. Rates of meeting MDD diagnostic criteria at the Intake Visit and Week 16 Assessment Visit will be used to compare group remission across time.

Suicide risk

Suicide ideation is a potential safety concern for participants given the study's population. Therefore, suicide risk will be formally monitored throughout the duration of the study via the Columbia-Suicide Severity Rating Scale (C-SSRS; [76]). The C-SSRS will be administered by trained Clinical Interviewers (i.e., certified in CSSRS Training for Clinical Practice) during each assessment visit and when warranted based on the study suicide safety plan.

Secondary outcomes

Middle cerebral artery blood velocity

Cerebrovascular outcomes will include MCA blood velocity measured non-invasively via a 2-mHz TCD

Table 1 Timing of assessments across the 16-week intervention and 52-week study involvement

	Intake Visit	Week 0 Visit	RET Sessions 1–3	Weeks 2–8	Week 8 Visit	Weeks 9–16	Week 16 Visit	Week 26 Visit	Week 52 Visit
Enrollment									
Informed Consent	X								
Eligibility Check	X								
Exercise Familiarization			X						
Randomization			X						
Intervention									
Low-Dose Group				X		X			
High-Dose Group				X		X			
Assessment									
Primary outcomes									
GRID-Hamilton Rating Scale for Depression	X				X		X	X	X
Quick Inventory for Depressive Symptoms	X	X	X	X	X	X	X	X	X
Structured Clinical Interviews for DSM-5 Disorders	X				X		X	X	X
Columbia Severity Suicide Rating	X				X		X	X	X
Secondary outcomes									
Cerebrovascular Mean Velocity		X			X		X	X	X
Cerebrovascular Pulsatility		X			X		X	X	X
Self-Efficacy		X	X	X	X	X	X	X	X
Baseline characteristics*	X								
Tertiary outcomes									
Anthropometric Assessments*	X								
International Physical Activity Questionnaire- SF		X			X		X	X	X
ActivPAL*		X			X		X	X	X
Short Form Health Survey 36		X			X		X	X	X
Penn State Worry Questionnaire		X			X		X	X	X
Perceived Stress Scale		X			X		X	X	X
Insomnia Severity Index		X			X		X	X	X
PROMIS Cognitive Function		X			X		X	X	X
Emotional Regulation		X			X		X	X	X
Big Five Inventory		X			X				
Rumination-Reflection Questionnaire		X			X				
Exercise Habits		X	X	X	X	X	X	X	X
Exercise Identity		X	X	X	X	X	X	X	X
Exercise and Health Questionnaire		X	X		X	X	X	X	X
Cerebrovascular Assessments*		X			X		X	X	X
Post-intervention measures*							X	X	X

* Baseline Characteristics: Demographics, Health History, DSM5 Level 1 Cross-Cutting Symptoms, World Health Organization Disability Assessment Schedule, Adverse Childhood Events, Patient Health Questionnaire- 9, Generalized Anxiety Disorder- 7

* Anthropometric Assessments: Height, Weight, and Body Composition

* ActivPAL: issued 1 week before visit, participant to wear it for 7 days and return it at the visit

* CV Assessments: Heart Rate, Vascular contributors to CBF, End Tital CO_2, CV Reactivity, Autonomic function, Blood Pressure Variability, Heart Rate Variability

* Post-Intervention: Patient Global Impression of Change, Subjective Treatment Satisfaction Survey (Post-intervention visit only), RET Follow-up Questionnaire, & Group Bias Questionnaire (Both at 26- and 52-week follow-up)

ultrasound probe secured to the temporal window via a headset, as conducted by our team previously [2, 4, 62, 72, 81, 105]. Cerebrovascular measurements will be taken in a dimly lit room under supine, resting conditions following 10 min of quiet rest. Measurements will be taken from the MCA at rest (primary outcome) and in response to a CO_2 challenge to stimulate increases in MCA blood velocity. MCA blood velocity will be calculated using a standard algorithm implemented on the instrument. Measurements will be completed at each assessment visit, with average change in MCA blood velocity at rest and in response to CO_2 from the Intake Visit to Week 16 Assessment Visit the primary timepoints of interest to examine differences between groups.

Cerebrovascular pulsatility

Cerebral pulsatility index will be measured using the same techniques and conditions described for MCA blood velocity and as also conducted previously [2, 4, 62, 72, 81, 105]. Pulsatility will be calculated via an automated waveform tracking function using the equation $(V_s\text{-}V_d)$/mean V, where V_s is the peak systolic velocity, V_d diastolic velocity, and mean V is the mean velocity. Measurements will also be taken at each assessment visit, with changes in mean cerebral pulsatility by group from the Week 0 to Week 16 Assessment Visit being the metric and timepoints of interest, respectively.

Self-efficacy

Self-efficacy is a key psychological mechanism of interest. As such, general self-efficacy will be measured via the New General Self-Efficacy Scale (NGSE; [13]). The NGSE is an 8-item instrument that uses a 5-point Likert scale (e.g., 1 = Strongly Disagree, 5 = Strongly Agree) to rate how confident the participant is at accomplishing scenarios (e.g., "I will be able to achieve most of the goals that I have set for myself"). The GSE is scored as an overall mean score with higher scores indicating greater levels of self-efficacy. Changes in group averages will be compared at each assessment visit, with primary timepoints being the Intake Visit to Week 16 Assessment Visit. The GSE has demonstrated high reliability ($\alpha = 0.88$; [13]) and has a strong positive association with the General Self-Efficacy Scale rated self-efficacy ($r = 0.90$, $p < 0.05$). In addition, because general self-efficacy may improve as a result from task-specific self-efficacy (i.e., RET task self-efficacy), this construct will also be evaluated by asking "How confident are you that you will be able to [resistance exercise] regularly in the next 2 weeks?" and "How confident are you that, over the next 2 weeks, you could overcome obstacles that prevent you from [resistance exercising] regularly?," with response choices ranging from "Not at all confident" (1) to "Very Confident" (5), with higher scores reflecting higher levels of reported RET task self-efficacy. Self-efficacy will be assessed at each assessment visit, with average changes in self-efficacy by group from Week 0 to the Week 16 Assessment Visit the metric and timepoints of interest, respectively.

Baseline characteristic outcomes

The measures in this section will be collected during the Intake Visit only to characterize the sample, use in data sharing reporting as required, or aid in examining predictors of treatment success.

Demographics and health history

Participants will report demographic information including race, gender, age, sex, ethnicity, education level, marital status, income, and employment status. In addition, participants will be asked to report current medication usage, mental health treatments (e.g., therapy, medication), and current and past health conditions (e.g., heart conditions, cancer, diabetes). Percents for each categorical variable (e.g., race) and means for each continuous variable (e.g., age) at Intake will be used to examine baseline group differences.

DSM-5 level 1 cross-cutting symptom measure

The DSM-5 Level 1 Cross-Cutting Symptoms Measure is a self-rated measure comprised of 23 questions used to evaluate mental health domains. Thirteen domains aid in psychiatric diagnosis [56], evaluating depression, anger, mania, anxiety, somatic symptoms, suicidal ideation, psychosis, sleep problems, memory, repetitive thoughts and behaviors, dissociations, personality functioning, and substance use over the previous 2-week period. Higher scores within these domains indicate possible problematic symptoms. Average continuous scores at intake will be used to examine baseline group differences.

World health organization disability assessment schedule

The World Health Organization Disability Assessment Schedule (WHODAS) is a self-rated measure consisting of 12 questions used to evaluate difficulties appearing due to health conditions including long-lasting health concerns, disease/illness, injuries, mental health problems, and substance use. This questionnaire evaluates the strain of carrying out everyday life tasks over the past 30 days. Response choices range from "None" (1) up to "Extreme or cannot do" (5), with higher scores indicating greater levels of difficulty due to a health condition. The score of each question is summed for a total score. Research has found this questionnaire to have high internal consistency ($\alpha = 0.81$–0.96) and correlations with other disability scales [84]. Average continuous scores at Intake will be used to examine baseline group differences.

Adverse childhood experiences

Adverse childhood experiences will be evaluated using the Adverse Childhood Experience Survey (ACES; [24]). The ACES consists of 16 questions pertaining to the respondents' first 18 years of life, in which participants respond with yes/no regarding the occurrence of the adverse event, with scores ranging from 0 (unexposed) to 7 (exposed to all categories). Total scores from the Intake Visit will be used to examine the influence of childhood experiences on treatment effects. Average continuous scores at Intake will be used to examine baseline group differences.

Patient health questionnaire-9

The Patient Health Questionnaire–9 (PHQ-9) assesses self-reported depressive symptom severity. The PHQ-9 is a 9-item self-report questionnaire that uses a 4-point Likert scale (e.g., 0 = Not at all, 3 = Nearly Every Day) to assess the presence and severity of depressive symptoms, with scores categorized as minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) [43]. The PHQ-9 has demonstrated excellent internal consistency ($\alpha = 0.89$) and is strongly correlated with the HAMD-17 in patients with MDD ($r = 0.61$, $p < 0.001$ [91];). Average continuous scores at Intake will be used to examine baseline group differences.

Generalized anxiety disorder-7

The Generalized Anxiety Disorder-7 (GAD-7; [90]) is a 7-item self-reported questionnaire in which participants use a 4-point Likert scale (e.g., 0 = not at all, 3 = nearly every day) to rate seven anxiety-related questions using the prompt "Over the last 2 weeks, how often have you been bothered by the following problems?". Scoring for the GAD-7 is obtained from the sum of all responses, with scores of 0–5, 6–10, and 11–15 serving as ranges for mild, moderate, and severe anxiety, respectively. The GAD-7 has demonstrated excellent internal consistency ($\alpha = 0.92$; [90]) and has a strong association with the Beck Anxiety Inventory ($r = 0.72$ [90];). Average continuous scores at Intake will be used to examine baseline group differences.

Tertiary outcomes

Anthropometric assessments

Anthropometric assessments will include height, weight, and a bioelectrical impedance analysis. A standard stadiometer and scale will be used to assess height and weight, respectively, during the Intake Visit to assess body mass index, as exclusionary criteria. During each subsequent assessment visit, a bioelectrical impedance analysis will be conducted to examine changes in weight, muscle mass, and fat mass. Mean changes in these metrics will be examined by group at the Intake Visit and Week 16 Assessment Visit (primary timepoints) and during follow-up visits.

Strength

Muscle strength assessments will be completed to program exercise workload and as a manipulation check of the RET intervention. Standard estimated 1RM procedures will be employed (e.g., [88]). Estimated 1RMs (continuous variable) will be completed on each exercise machine during the familiarization period. Leg press, chest press, and lat pull down will be the primary strength indicators in this trial to examine average group changes in strength from baseline assessments and the Week 16 Assessment Visit (primary timepoints of interest), as well as the 26- and 52-Week Assessment Visit.

Grip strength will be collected for a simple, quick, overall estimate of strength, assessed using a hydraulic hand dynamometer (Jamar Plus + 12–064; Lafayette Instrument). Participants will squeeze the dynamometer twice to practice. Then, three trials will be completed on each hand by squeezing the device as hard as possible. Grip strength will be measured at each assessment visit. Group means (as continuous variables) will be used to compare differences from Week 0 Assessment Visit and Week 16 Assessment Visit (primary timepoints of interest), as well as the 26- and 52-Week Assessment Visits.

Blood biomarkers

Changes in blood-based biomarkers (e.g., endocannabinoid, brain-derived neurotrophic factor, pro-inflammatory cytokines) may relate to the effect of RET on MDD. As such, blood samples will be collected at the beginning of each assessment visit and stored to evaluate alternative mechanisms associated with or potentially underlying treatment responses. Plasma and serum samples (one 10 ml tube each) will be collected and stored at − 80 °C until future analyses are conducted. The average group change in biomarkers of interest will be compared from Week 0 to Week 16 Assessment Visit (primary timepoints of interest), as well as the 26- and 52-Week Assessment Visit.

Physical activity and sedentary time

Self-reported physical activity and sedentary time will be assessed via the International Physical Activity Questionnaire-Short Form (IPAQ-SF; [20]). The IPAQ-SF will be administered verbally at each assessment visit, inquiring

about amounts of vigorous activity, moderate activity, and walking over the past 7 days, and average hours of sitting on a weekday. Moderate to vigorous physical activity (MVPA) and MET minutes per week as continuous variables will be calculated from responses using standard scoring procedures, and average changes in those activity patterns by group from the Intake Visit to Week 16 Assessment Visit will be primary timepoints of interest. The IPAQ-SF has previously demonstrated high reliability ($\alpha < 0.80$; [20]).

Activity levels will also be measured via accelerometry (activPAL4, PAL Technologies Ltd., Scotland, UK). The activPAL is a small triaxial accelerometer that uses thigh position to classify physical activity as sedentary, upright, or stepping. Participants will be instructed to place the device on the midline of the thigh for 7 days (24 h/day), removing only for water-based activities (e.g., swimming, bathing), and be given a log sheet and asked to record sleep time and when the monitor was on/off. Monitor data will be processed and analyzed with activPAL proprietary software (i.e., PALconnect, PALanalysis). This monitor has demonstrated high reliability and validity for differentiating between and measuring physical activity and sedentary time in free-living conditions [42, 69]. Continuous data (e.g., average MVPA, sitting time, steps per day) will be averaged by group and compared at Intake and Week 16 Assessment Visit as primary timepoints of interest.

Quality of life

The SF-36 Health Survey (SF-36; [100]) will be administered to assess quality of life. The SF-36 is a 36-item questionnaire that assesses health status through eight health dimensions: (1) Physical functioning, (2) Social functioning, (3) Physical role limitations, (4) Emotional role limitations, (5) Mental health, (6) Vitality, (7) Pain, and (8) General health perception. Subscale scores for each dimension will be calculated using standardized scoring, and group total score means (as a continuous variable) will be used to examine changes in quality of life at each assessment visit, with primary timepoints being the Week 0 and Week 16 Assessment Visits. Across the eight dimensions of health, internal consistencies within depressed adults ranged from 0.60 to 0.92 ($\alpha = 0.79$; [80]).

Worry

Worry symptoms will be assessed via the Penn State Worry Questionnaire (PSWQ; [63]). The PSWQ is a 16-item questionnaire that uses a 5-point Likert scale (e.g., 1 = Not at all typical of me, 5 = Very typical of me) to assess worry symptoms. Scoring for the PSWQ is obtained by summing the responses, obtaining a total score ranging from 16 to 80, with higher scores indicating more worry. Averages of the total scores (as a continuous variable) will be used to examine group differences at all timepoints, with Week 0 and 26 Assessment Visits as the primary timepoints. The PSWQ has demonstrated strong reliability ($\alpha = 0.95$ [6];) and is positively correlated with the State-Trait Anxiety Inventory ($r = 0.64$, $p < 0.001$; [63]).

Stress

The 10-item Perceived Stress Scale (PSS-10; [14]) will be used to assess self-reported stress level. The PSS-10 is a 10-item questionnaire using a 5-point Likert scale (e.g., 0 = "Never", 4 = "Very Often" for negatively stated items, and 0 = "Very Often", 4 = "Never" for positively stated items) to assess how unpredictable, uncontrollable, and overloading life has been over the past month. Items are summed to calculate a total score ranging from 0 to 40, with high scores indicating higher received stress. Group means of the total score (as a continuous variable) will be used to examine changes in stress across the study, with the Intake Visit to Week 16 Assessment Visit as primary timepoints. The PSS-10 has acceptable psychometric properties, with $\alpha > 0.70$ in 12 studies examining test–retest reliability and criterion validity compared to common stress measures (e.g., PSS-14, STAI; [48]).

Insomnia

The Insomnia Severity Index (ISI; [67]) will be administered to assess current insomnia severity. The ISI is a 7-item self-report questionnaire assessing current (i.e., last 2 weeks) severity of insomnia symptoms and sleep-related impairments to quality of life. The ISI uses a 5-point Likert scale to rate: the severity of symptoms (e.g., 0 = None; 4 = Very Severe), the participant's satisfaction with current sleep patterns (e.g., 0 = Very Satisfied; 4 = Very Dissatisfied), the perception of noticeability of sleep impairments to quality of life to others (e.g., 0 = Not at all Noticeable, 4 = Very Much Noticeable), psychological distress due to sleep disorder (e.g., 0 = Not at all Worried, 4 = Very Much Worried), and interference with daily functioning (e.g., 0 = Not at all Interfering, 4 = Very Much Interfering). Scoring for the ISI is obtained from the sum of all responses, with scores of 0–7, 8–4, 15–21, and 22–28 serving as thresholds for no clinically significant insomnia, subthreshold insomnia, clinical insomnia of moderate severity, and severe clinical insomnia, respectively. Group averages of the total scores (as a continuous variable) and percent of insomnia by category will be used to examine the influence of the intervention on sleep quality by group, with Week 0 and Week 16 the

primary timepoints of interest. The ISI has previously been found to have high internal reliability and is significantly correlated with the Pittsburgh Sleep Quality Index ($r = 0.80$, $p < 0.05$; [67]).

Cognitive functioning

Cognitive function will be assessed via the Patient-Reported Outcomes Measurement Information System Cognitive Function questionnaire (PROMIS-CF; [46]). The PROMIS-CF is a self-reported 6-item instrument that uses a 5-point Likert scale (e.g., 5 = Never, 1 = Very often (Several times a day)) to rate the frequency of current (i.e., "In the past 7 days") cognitive impairments. The PROMIS-CF is scored by summing the values of each response, with higher scores indicating greater cognitive impairment. Group means of continuous scores will be used to examine group differences at each assessment visit, with Week 0 and Week 16 as primary timepoints. The PROMIS-CF demonstrates very high reliability ($\alpha = 0.96$) and is strongly associated with PHQ-9 assessed symptoms of depression ($r = 0.617$, $p < 0.01$; [94]).

Emotional regulation questionnaire

Emotional regulation will be assessed via the emotional regulation questionnaire (ERQ; [31]). The ERQ is a 10-item questionnaire that uses a 7-point Likert scale (e.g., 1 = strongly disagree, 7 = strongly agree) to assess the participant's tendency to regulate their emotions in two ways: (1) cognitive reappraisal and (2) expressive suppression. The ERQ is scored by separately summing the score for elements pertaining to each facet, with higher scores on each indicating better emotional regulation. Group mean of continuous scores for each facet will be calculated at assessment visits to examine group differences. The ERQ has acceptable to excellent levels of internal consistency reliability for cognitive reappraisal ($\alpha = 0.89$–0.90) and expressive suppression ($\alpha = 0.76$–0.80 [78];), with cognitive reappraisal negatively correlated ($r = -0.32$, $p < 0.001$) and expressive suppression positively correlated ($r = 0.18$, $p < 0.001$) with depression [77].

Personality

Personality will be assessed using the Big Five Inventory (BFI; [39]). The BFI is a 44-item questionnaire that uses a 5-point Likert scale (e.g., 1 = Disagree strongly, 5 = Agree Strongly) to measure an individual on the five dimensions of personality (i.e., Openness, Neuroticism, Conscientiousness, Agreeableness, and Extraversion). The BFI will be administered at week 0 and 16 to examine the influence of personality on treatment effects of the intervention, using continuous total scores for each dimension of personality. Across the five dimensions of personality, the BFI has been shown to be reliable ($\alpha = 0.83$; [39]).

In addition, rumination specifically will be assessed via the Rumination-Reflection Questionnaire (RRQ; [93])). The RRQ consists of 24 items inquiring about ruminative vs reflective attentional focus, in which participants indicate their level of agreement on each item using a 5-point scale, ranging from "Strongly disagree" (1) to "Strongly Agree" (5). Averages of items 1–12 are used to calculate a Rumination score, and averages of items 13–24 are used to calculate a Reflection score. Group means of continuous scores will be used to examine differences specifically at weeks 0 and 16, along with the BFI. The RRQ has high internal consistency ($\alpha > 0.90$) and highly correlated with the Self-Consciousness Scale [93].

Exercise habits

An exercise habits questionnaire will be used to assess the automaticity of preparing for, instigating, and executing RET sessions. Four items from the Self-Reported Behavioral Automaticity Index, which is itself a subset of items from the Self-Reported Habit Index (SRHI; [28, 71, 95, 96]), will be used to assess each type of habit (preparation to exercise, instigating exercise, executing exercise). The scale uses a 5-point Likert scale (e.g. 1 = Strongly disagree, 5 = Strongly agree). For preparation habits: "Preparing what I need to [do a resistance exercise workout] is something I do automatically", "…I do without having to consciously remember", "…I do without thinking," and "…I start doing before I realize I'm doing it." For instigation habits: "Going to [a resistance exercise workout] is something I do automatically", "…without having to consciously remember", "…without thinking", and "…I start doing before I realize I'm doing it." For execution habits: "Once I have begun [doing resistance exercises, going through a sequence of movements (for example, switching from my first exercise to the second)] is something I do automatically", "…without having to consciously remember", "…without thinking", and "…I start doing before I realize I'm doing it." Mean scores for each subscale will be computed, with higher scores indicating stronger habits. Group means for each subscale continuous score will be used to explore differences in exercise habit strength at all assessment visits, with Week 0 and Week 16 primary timepoints of interest.

Exercise identity and intrinsic motivation

Items from subscales in the Behavioural Regulations in Exercise Questionnaire [58] and Exercise Identity Scale [3] will be used to examine changes in exercise identity and intrinsic motivation, known to relate to exercise adherence. Ten items are used and rated on the Likert scale, not true for me (1) to very true for me (5), adapted to be specific to resistance exercise training (e.g., "Resistance exercise is a central factor to my self-concept").

Higher scores on exercise identity and intrinsic motivation subscales indicate greater feelings of self-identity as an exerciser and motivation, respectively. Group means for each subscale continuous score will be used to explore differences at all assessment visits, with Week 0 and Week 16 primary timepoints of interest.

Exercise and health questionnaire

To assess participant expectations for how RET will make them feel short and long term, an exercise and health questionnaire (EPOES) will be administered. The EPOES is a 15-item self-report questionnaire using a 7-point Likert scale (e.g., 1 = large decrease, 7 = large increase) inquiring about perceived effects of RET on specific health-related outcomes (e.g., fatigue, mood, ability to relax, pain) compared to how participants generally feel. A chronic and acute version will be administered to assess immediate and long-term effects. The chronic EPOES will use the prompt, "Think about how you would expect to feel after completing a resistance exercise program 2 sessions per week for 8–12 weeks relative to how you typically feel." The acute EPOES will use the prompt, "Think about how you would expect to feel after one resistance exercise workout relative to how you typically feel." The chronic EPOES will be administered during all assessment visits (primary timepoints Week 0 and Week 16 Assessment Visit) and the acute EPOES will be administered during the first regular RET session (i.e., Session 4, after familiarization) and final RET sessions (i.e., Session 31). Group means will be used to examine group differences for both acute and chronic at the specified time points.

Patients' global impression of change

The Patient's Global Impression of Change scale (PGIC; [38]) will be administered to assess the degree of change regarding activity limitations, symptoms, emotions, and overall quality of life perceived by the participant. The PGIC consists of one item that uses a 7-point Likert scale (e.g., 1 = No change, 7 = A great deal better, and a considerable improvement that has made all the difference) to assess change using the prompt: "Since beginning the study, how would you describe change (if any) in Activity Limitations, Symptoms, Emotions, and Overall Quality of Life, related to your condition?" This question is followed by a visual analog scale (ranges from 0 = Much Better to 10 = Much Worse) to assess the participants' perception of their degree of change. The mean scores for each question will be compared separately as group means at assessment visits after the completion of the intervention (i.e., weeks 16, 26 and 52), with Week 16 the primary timepoint of interest. Scores on the PGIC have been associated with changes in PHQ-9 rated symptoms of depression following treatment previously ($r = 0.45$, $p < 0.001$, [85]).

Subjective treatment satisfaction

Acceptability, appropriateness, and feasibility of study implementation of RET for treatment of MDD will be assessed using (1) Acceptability of Implementation Measure (AIM), (2) Implementation Appropriateness Measure (IAM), and (3) Feasibility of Intervention Measure (FIM) [102]. Four items will be used to assess each outcome with response choices ranging from 1 (Completely Disagree) to 5 (Completely Agree), with higher total scores indicating higher satisfaction with the treatment provided. Average continuous scores from Week 16 Assessment Visit will be used as the primary timepoint to explore intervention satisfaction by group. These measures have previously demonstrated high validity, reliability, and response to change [102].

Cardiovascular and cerebrovascular assessments

The following cardio- and cerebrovascular assessments will be completed to supplement and contextualize primary mechanistic targets. These outcomes will be analyzed as continuous variables, examining mean group differences between the Week 0 and Week 16 Assessment Visits, with enduring effects examined in subsequent Assessment Visits.

Blood pressure measurements will be taken after 10 min of quiet rest at the brachial artery (i.e., upper arm) using a standard automated, oscillometric blood pressure cuff. Brachial blood pressure will be taken three times and averaged. If readings differ by > 5 mmHg, blood pressure will be re-assessed until 2 values are obtained within 5 mmHg.

During the cerebrovascular assessments, end-tidal CO_2 ($ETCO_2$) will be measured via capnography, and beat-to-beat blood pressure will be assessed continuously via photoplethysmography. Cerebrovascular reactivity to CO_2 assessed from the rate of change in MCA blood velocity relative to the rate of change in $ETCO_2$ during the CO_2 challenge [4, 19]. Participants will breathe 4% and 6% CO_2 from pre-mixed medical gas tanks. Each level will be sustained for 3 min to achieve a steady state. MCA blood velocity will be assessed during these transient changes in CO_2. The average MCA blood velocity will be measured during the final 60 s at each stage as previously described. Changes in group means for all cardiovascular and cerebrovascular assessments will be used to compare groups at all assessment visits. Volumetric cerebral blood flow of the intracranial arteries will be assessed using duplex ultrasound.

Arterial stiffness will be assessed at the aorta and carotid artery. Aortic stiffness will be measured using gold-standard procedures as carotid-femoral pulse wave velocity via applanation tonometry [5, 25, 65, 74]. Carotid stiffness will be determined via ultrasound measurement of carotid distension waveforms, and carotid pressures obtained from contralateral carotid tonometry as previously described [51, 68, 81]. We will also noninvasively assess cardiac autonomic function via heart rate variability and blood pressure during 5 min of beat-to-beat heart rate (3-lead ECG) and blood pressure (finger photoplethysmography) acquisition as previously described [37]. Further, grip strength will again be assessed. Participants will rest quietly prior to squeezing the dynamometer for several minutes (or until fatigue). Immediately after, a blood pressure cuff will be placed on the testing arm and inflated to 100 mmHg suprasystolic for 90 s to test the metaboreflex.

Study timeline

Participant timeline {13}

Overall study flow is displayed in the CONSORT diagram in Fig. 1.

Screening

Individuals interested in participating will first complete an online pre-screening survey to assess initial eligibility based on age, BMI, mental health status, and current depression symptom severity (PHQ-8 $\geq$ 10; [44]). If potentially eligible, participants will be contacted by research staff to verify initial eligibility, answer questions about study enrollment, and schedule an Intake Visit.

Intake visit

During the Intake Visit, participants will first complete the informed consent process (detailed above). Height and weight will then be measured to assess BMI

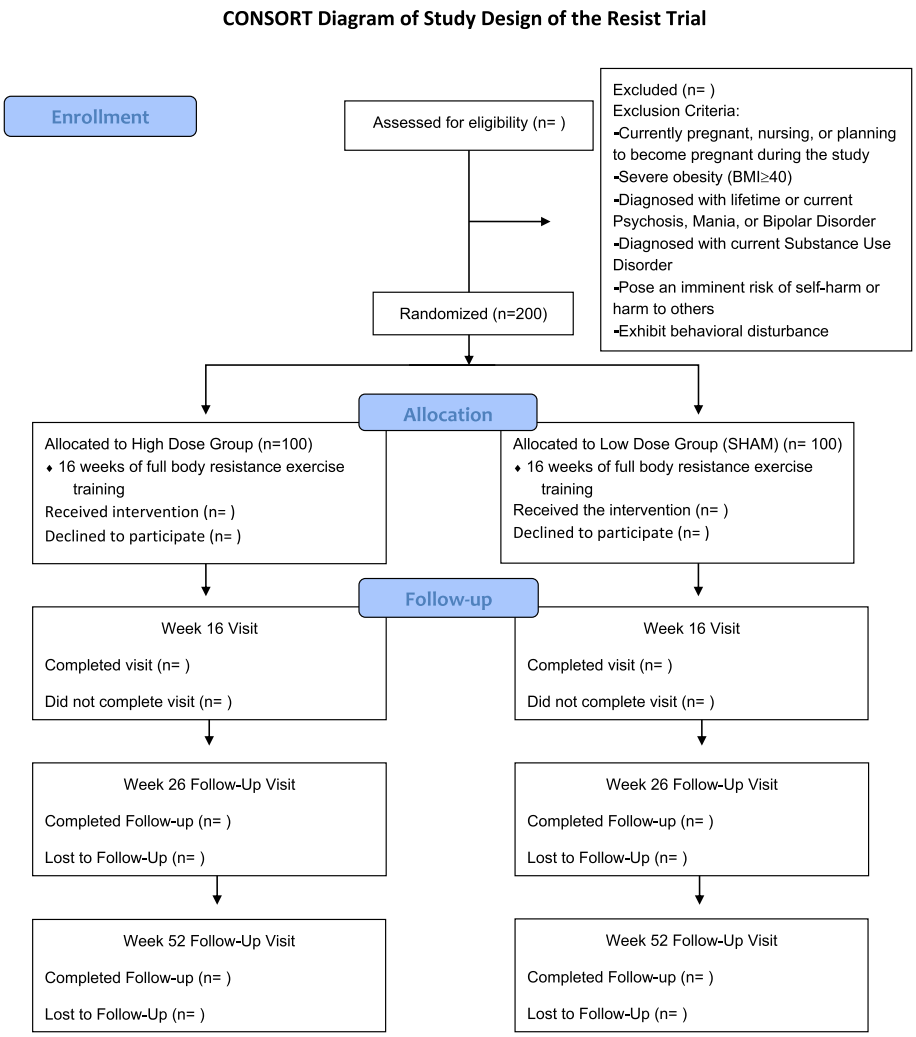

Fig. 1 CONSORT diagram of study design of the resist trial

(exclusionary criteria). Next, participants will then complete questionnaires electronically on REDCap, which will include health history, mental health treatment, DSM5, WHODAS, PHQ9, GAD7, ACE, and QIDS. Then, participants will complete a mental health interview with a Clinical Interviewer. The Clinical Interviewer will administer the SCID to screen for current MDD and assess for the presence of exclusionary psychological diagnoses. The following sections of the SCID will be completed: (1) Nonpatient overview, used to build rapport with the Clinical Interviewer, (2) Mood Episodes, to confirm a current MDD diagnosis and screen for current or lifetime Mania, (3) Psychotic and Associated Symptoms, to screen for current or lifetime diagnosis of Psychosis or Bipolar Disorder, (4) Substance Use Disorders, to screen for current substance use disorder, and (5) Anxiety Disorders, to document co-occurring anxiety disorders due to high comorbidity. Following the SCID-R, the Clinical Interviewer will also administer the GRID-HAMD and C-SSRS to assess depressive symptom severity and suicide risk, respectively. Participants who are diagnosed with MDD and without other exclusionary psychological diagnoses from the SCID-R have at least mild symptoms of depression from the HAMD (score ≥ 8), and scores < 5 on the C-SSRS will be eligible to enroll in the study. Finally, participants will be provided with instructions on the use of an activPAL accelerometer and asked to wear the device on their thigh for 7 days (24 h/day) to assess their physical activity and sedentary behaviors and subsequently return for a Week 0 Assessment Visit.

Week 0 assessment visit

Participants will attend the Week 0 Assessment Visit following 24-h abstinence from alcohol, exercise, and dietary supplements; at least 4 h fasting; and not consuming nonessential medication or caffeine the day of testing, as these activities and substances can influence artery function. During the visit, participants will have a blood sample collected and complete questionnaires (i.e., IPAQ-SF, PSWQ, PSS, SF-36, QIDS, EIQ, General Self-Efficacy Scale, RET-Specific Self-Efficacy Scale, ISI, PROMIS Cognitive Function—short form, ERQ, Exercise Habits Questionnaire, and chronic EPOES). Participants will have cerebrovascular assessments taken (described above), along with body composition assessment, grip strength testing, and familiarization with exercise equipment. They will receive health education to identify intrinsic motivations for RET, create preparatory exercise habit and coping plans, and document commitment to the intervention (i.e., 0–100% slider of commitment, yes/no response to attending next session, signature confirming responses). Finally, all RET sessions and assessment visits will be scheduled.

Familiarization sessions (RET Sessions 1–3)

The first three RET Sessions will serve as a run-in period, in which participants will go through familiarization on all machines in the same order, complete one rep max (1RM) testing on each machine, and be given instructions for an at-home exercise band workout to complete when unable to attend sessions in person (e.g., traveling, holidays). During these three RET Sessions, participants will complete 1RM testing on the chest press, lat pulldown, leg press (three primary strength outcomes), and on the rest of the machines (leg curl, row, triceps, leg extension, military press, and arm curl). Upon completion of all familiarization processes and exercise testing (i.e., at the end of RET session 3), participants will be randomized to either the High-Dose or Low-Dose group.

RET sessions

During the remainder of the 16-week intervention period, participants will complete RET sessions twice per week (~1 h/session). At the beginning of the first session each week, participants will complete the QIDS electronically via REDCap to assess depressive symptoms and monitor suicidality. Weekly, they will also complete questions related to exercise adherence (e.g., motivations for exercise, habit development, commitment). They will then be given a personalized workout (i.e., prescribed exercises and workloads) based on their group assignment (described above).

All exercises will be performed using state-of-the-art resistance exercise machines. Each session will last ~60 min and begin with a 5-min warm-up consisting of an aerobic activity (walk/jog on treadmill, use elliptical or cycle ergometer, or outdoor walking/jogging) and stretching. Participants will then perform 3 sets of 8–12 repetitions on each exercise machine (i.e., leg press, hamstring curl, quadriceps extension, chest press, upper back, lat pulldown, shoulder press, biceps curl, and triceps extension) and 3 sets of abdominal exercises (i.e., planks or abdominal crunches). Each exercise will have a 30-s rest time between each set, except for leg press which will have a 1-min rest time between sets. A research team member will be present to monitor form and answer questions during each session. When individual participant circumstances dictate (e.g., pain with certain movement/range of motion), modifications will be made that minimize alterations to the prescribed workout (e.g., switching from machine to free-weight exercise while keeping the same movement).

Week 8, 16, 26 and 52 assessment visits

Participants will return for Assessment Visits during weeks 8, 16, 26, and 52, respectively, after re-wearing the activPAL activity monitor for 7 days. Strength assessments (i.e., 1RM testing) for three large-muscle lifts that comprise our primary strength measures (i.e., chest press, lat pulldown, and leg press) will be completed during the preceding RET Session or in conjunction with the assessment (i.e., on weeks 26 and 52). All other assessments will be identical to Intake Visit and Week 0 Assessment Visit procedures. Each will begin with a clinical interview by a trained Clinical Interviewer assessing current MDD, symptom severity, and suicidality via the SCID, HAM-D, and C-SSRS Since Last Visit, respectively. Next, a blood draw will be taken. Questionnaires will then be administered and include questionnaires from the Week 0 Assessment Visit. Following this, cerebrovascular measures, body composition, and grip strength will be completed. During the Week 16 Assessment Visit, participants will also complete the Satisfaction Survey and Adverse Event Assessment (to proactively monitor reportable events). The PGIC will also be administered at the 16-, 26-, and 52-Assessment Visits. Participants will conclude study enrollment upon completion of the 52-Week Assessment Visit.

Sample size {14}

SAS (version 9.4 or newer) and R (version 4.4 or newer) were used to determine sample size and will be used for all analyses. This trial is powered to detect a minimum clinically important difference (MCID) of 4 points in GRID-HAMD between the RET and SHAM groups. According to Moncrieff and Kirsch [66] the standard deviation of changes in HAMD during treatment is 8.0, such that a 4-point MCID translates to a medium effect size (Cohen's $d = 0.5$). Enrolling and retaining 172 participants would achieve 90% power to detect this effect. However, we will enroll 200 participants to insure against up to 15% attrition. The power analysis is conservative because we will adjust analyses for prognostic covariates (e.g., baseline HAMD score, gender, sex, and severity) so that the conditional standard deviation is likely to be smaller than 8 points.

Recruitment {15}

The primary mode of recruitment will be referrals from local hospitals, clinics, and outpatient mental health treatment centers. This will be accomplished via direct patient referral from physicians, electronic health records, and health system research partners. These methods will be supplemented by mass emails to the university community and large local employers, community flyers, and social media posts.

Assignment of interventions: allocation

Sequence generation {16a}

Sex (male/female), medication-usage (yes/no), and severity-stratified (mild vs. moderate-severe on GRID-HAMD) 1:1 permuted block randomization will occur during RET Session 3 after all baseline data are collected.

Concealment mechanism {16b}

The randomization module on REDCap will be used to implement the allocation sequence. The necessary allocation tables will be pre-generated by the study statistician and uploaded to the REDCap randomization module.

Implementation {16c}

Senior research staff will enter required fields on REDCap (i.e., symptom severity level, sex, medication usage) at the end of RET Session 3 after all baseline data are collected. When complete, the team will select "Randomize," which will automatically generate the group assignment based on the uploaded randomization schedule and stratification variables.

Assignment of interventions: blinding

Who will be blinded {17a}

The principal investigator, blinded statistician, and outcome assessors (e.g., cerebrovascular assessors, clinical interviewers, strength assessors) will be masked to participant assignment until the pre-specified analyses have been completed. To systematically monitor incidental group disclosure, all outcome assessors will record any conversations with participants in which the group was disclosed on REDCap, so analyses can be performed with and without those cases.

Procedure for unblinding if needed {17b}

Participant group assignment may be unblinded during the trial if requested by the Data Safety Monitoring Board (DSMB) after reviewing interim analyses in DSMB reports. As group assignment is unlikely to affect clinical decision making (as may be the case in investigational drug trials), it is anticipated that unblinding requests from the DSMB will be very infrequent and likely will not occur at all.

Data collection and management

Plans for assessment and collection of outcomes {18a}

To ensure data quality of clinical interviews, Clinical Interviewers will undergo substantial training (e.g., read instrument manuals, supporting literature, view mock interviews, role-playing) prior to completing a test-out with a standardized participant, requiring high

agreement between their and the Clinical Team supervisor's assessment on each measure (i.e., SCID, C-SSRS, GRID-HAMD). To ensure data quality for CV assessments, all assessors will complete comprehensive training (e.g., direct observation, practice trials on diverse people) and reliability testing prior to administering CV tests. Further, all CV measures will be taken in duplicate. Both the CV and Clinical Interviewers will subsequently undergo regular monitoring by their associated supervisor. All additional assessment and data collection plans, including psychometric properties of each study instrument, are detailed above.

Plans to promote participant retention and complete follow-up {18b}

Participant retention will be promoted in several ways, including using unique study identifiers (e.g., logo, colors, font in all study materials and participant communications), thorough informed consent procedures (e.g., easy-to-understand visual representations of study visits and procedures, tour of research facilities), offering flexible scheduling, reimbursement for travel to and from RET sessions, compensation for attending assessment visits, incentives for milestones of progress across the intervention (e.g., tee-shirts, water bottles), and having specific points of contact for each participant who will engage in scheduling, sending reminders, and being at each exercise session.

Data management {19}

All data will be collected and stored on REDCap and backed up with secure cloud storage, with both platforms only accessible to authorized research personnel. Data from each study visit will be electronically administered from REDCap (e.g., informed consent signature, questionnaires), manually entered to the platform (e.g., anthropometric assessments), or imported after the study visit (e.g., activPAL, cerebrovascular assessments). Data validations (e.g., numerical ranges, response format) will be set for each instrument to ensure data quality. Further, the Data Quality application on REDCap will be used to assess data missingness for all instruments, coupled with weekly reports generated in R to assess study progress and data quality and missingness of primary outcomes. All data will be stored for 1 year after study completion, and only de-identified data retained subsequently.

Confidentiality {27}

Unique study identifiers (e.g., RESIST 505) will be used on all study data to ensure confidentiality. One key will be kept on REDCap linking the unique study identifier to personal identifiable information. Restrictions will be set so only senior research personnel will be authorized to view the personal identifiable information, and all identifiers will be flagged to prevent all users from exporting identifiers from the platform. All personal identifiable information will be deleted from REDCap upon study completion.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood samples will be collected and stored for future analysis. All analyses of biological biospecimens (now and in the future) will be related to mental health or exercise response biomarkers. In all analyses, only de-identified data will be used (i.e., no personally identifying information will be associated with biological samples).

Statistical methods

Plans for assessment and collection of outcomes (Statistical methods for primary and secondary outcomes {20a}

Primary outcomes evaluating effects of High-Dose vs Low-Dose on MDD symptoms as measured by GRID-HAMD at each time point (8, 16, 26, and 52 weeks) will be evaluated using repeated-measures linear mixed effects models with the primary efficacy endpoint at week 16. The fixed effects will include group (RET, SHAM), time, group by time interaction, and other covariates (i.e., age, sex, severity or others from secondary data). Effect sizes (Hedges' g) will also be used to examine GRID-HAMD difference between High- vs Low-Dose at all time points. The trend of GRID-HAMD over time for both groups and the interaction effect between group and time will be examined. Similar analyses will be performed for additional clinical outcomes (i.e., SCID, QIDS).

Secondary outcomes (MCA blood flow velocity and cerebral pulsatility) will be evaluated using linear models with group effects and adjustments for other covariates. Mediation analyses will be carried out to assess the extent to which changes in cerebral blood flow velocity and pulsatility serve as mediators of the effects of RET on the HAM-D and the extent to which the HAM-D reduction (or other depressive symptom reductions) is explained by RET through cerebrovascular function.

Interim analyses {21b}

Limited interim analyses will be completed to evaluate trial progress, protocol adherence, and safety data (e.g., adverse event reporting) every 6 months and reported to the DSMB. No interim analyses will be performed on

primary or secondary outcome data, unless requested by the DSMB in consultation with the funder.

Methods for additional analyses {20b}

Additional analyses will identify stable and modifiable predictors of clinical change, mechanistic change, and adherence. For antidepressant responses (measured by GRID-HAMD) and for cerebrovascular responses (cerebral blood velocity and pulsatility), we will first evaluate interaction effects between groups (High- vs Low-Dose) and participant characteristics (such as severity, age, sex, or other demographic variables) to identify participant characteristics that may interact with treatment efficacy using linear mixed effects model analysis. Fixed effects in the model include group, covariates, and interactions between group and covariates. Second, we will evaluate the effects of potential moderators (all covariates we collect, including age, sex, baseline HAMD, stress, worry, etc.) on distinguishing those who preferably respond to High-Dose from those who preferably respond to Low-Dose using dimension reduction and moderator selection procedures. Third, we will employ machine learning methods (i.e., penalized regression methods such as LASSO, partial least square regression, and random forests) to select covariates that predict RET treatment successes/failures (based on clinical and CV outcomes) at 16 weeks, and cross-validation will be used to select the best models.

Methods in analysis to handle protocol non-adherence and methods for handling missing data {20c}

All primary analyses will be carried out according to the intention to treat principle using all randomized participants. All data collected prior to a participant's withdrawal will be incorporated into analyses when feasible. Missing outcome values will be multiply imputed with analyses pooled using Rubin's rules. The imputation models will include prognostic baseline covariates, randomization group, and outcomes at the previous assessment. Sensitivity analyses using all observed data (i.e., without imputation) will be carried out as well, and the reason for any substantive differences will be explored, including by assessing differences in baseline characteristics between participants with and without missing values. Data will be screened for outliers, and normality will be assessed by diagnostic plots and by the Kolmogorov–Smirnov test prior to analyses.

Plans to give access to the full protocol, participant level data and statistical code {31c}

Deidentified participant level data will be shared with and available from the National Institute of Mental Health Data Archives.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The institution the grant is awarded to will serve as the Coordinating Center, with the associated Institutional Review Board (IRB) serving as the IRB of record for the trial. A Data Safety Monitoring Board (DSMB) will be used to review trial progress and safety (detailed below).

Composition of data monitoring committee, its role and reporting structure {21a}

The university IRB will closely monitor study procedures and ethics, meeting biweekly to discuss all reported protocol modifications and reportable events. All submitted reports and IRB determination letters will subsequently be reported to a study-specific DSMB. The DSMB has been formed to independently monitor participant safety, data quality, and progress of the trial. The DSMB includes an Exercise Psychologist with expertise in depression (chair), a Clinical Psychologist (member), a clinical trials Biostatistician (member), and a Cardiologist (member). The DSMB will meet every 6 months throughout participant enrollment in the study. All reports and recommendations from the IRB and DSMB will also be reported to the study sponsor for review.

Adverse event reporting and harms {22}

Reportable events (e.g., adverse events, serious adverse events, protocol deviations, noncompliance) will be systematically documented by the research staff at all study visits during the intervention period. At the conclusion of each intervention study visit, research staff will mark "Yes" or "No" based on if a reportable event was reported by a participant. If a participant reports that a reportable event did occur during communication with the study team, a senior research staff will interview the participant to gather all information necessary to complete a Reportable Event Monitoring Form. In addition, to proactively monitor adverse events, participants will complete an Adverse Event Assessment every two weeks during the intervention. Information from this assessment will be used to systematically classify all reported events using MedDRA [11]. All data from adverse event monitoring will be timely reported to all necessary monitoring bodies (e.g., IRB, DSMB, NIH) and reported in subsequent publications, in addition to resulting protocol changes.

Frequency and plans for auditing trial conduct {23}

The IRB may perform post-approval monitoring as an annual audit of trial conduct. Monitoring will consist of an in-person review of all study records, data

storage, and security processes, with a formal report subsequently generated of monitoring findings and recommendations for improving study compliance.

Plans for communicating important protocol amendments to relevant parties {25}

Prior to implementation, all study modifications will be submitted for review to the IRB. Important protocol amendments will also be discussed with the study sponsor and DSMB, as well as formally documented in regular reports.

Dissemination plans {31a}

Trial results will be made available to healthcare professionals, the public, and other research teams on ClinicalTrials.gov, in manuscripts of primary and secondary outcomes, and presentations at national conferences. Deidentified study data will also be available from the National Institute of Mental Health Data Archives.

Discussion

Based on the ORBIT model for developing behavioral treatment [21], this phase III confirmatory efficacy trial will test High-Dose vs. SHAM/Low-Dose for treatment of MDD. If results favor RET, this trial lays the foundation for a Phase IV multi-site effectiveness trial for RET to be used as a standalone treatment, building toward the prescription of RET in clinical settings comparable to other frontline treatments (e.g., medication, therapy). Importantly, successful results may also provide rationale for evaluating the utility of RET for in the treatment of other mental illnesses. Further, comparative efficacy testing may be warranted to identify which treatment approach is most efficacious (e.g., RET vs aerobic exercise vs meditation vs medication). Finally, results of this trial will help move precision medicine forward by evaluating the predictive strength of participant characteristics and modifiable factors for both mechanistic and antidepressant effects, allowing for future prescriptions to be tailored to specific individuals or modifiable predictors to be targeted in future trials.

Understanding the mechanisms through which RET influences depression would be a powerful contribution to implementing and optimizing RET for treatment of MDD. This trial is designed to test leading physiological mechanisms (e.g., cerebrovascular hemodynamics) and psychological mediators (e.g., self-efficacy [SE]) known to be associated with depression symptoms and modifiable by RET. While MDD patients often exhibit lower cerebral perfusion [18, 23, 27] and previous studies show RET is associated with CBF in healthy populations [19, 49], no studies have comprehensively examined cerebrovascular changes from RET in individuals with MDD. Similarly, SE is related to depression [64], and RET may elicit antidepressant effects by increasing SE (e.g., self-mastery, competence-building experiences), yet this possibility is also understudied. Importantly, while cerebrovascular variables and SE are moderators of interest, this study will also collect data of other potential mechanisms (e.g., sleep, cognitive function, blood biomarkers) which will allow for additional exploratory analyses and substantially add to the limited body of literature of mechanisms by which RET may improve MDD.

Overall depression improvements and remission rates would improve substantially if the optimal treatment were designed and prescribed for each patient. This trial will use machine learning approaches to identify individual characteristics that predict immediate and long-term changes in depression, changes in mechanistic targets, and behavioral treatment adherence. Such models may be helpful in identifying response phenotypes (e.g., no/low/high benefit) from RET that could be used in clinical settings to identify individuals who may and may not benefit from RET as a treatment for DEP. Further, with adherence as a primary barrier to exercise as treatment for DEP, adherence modeling may help understand who is likely to adhere to behavioral interventions and which theoretical constructs (e.g., habit, self-efficacy) best facilitate adherence.

This study protocol has notable strengths, though it is not without limitations. Due to the potential confounding effects of social interactions with team members and the duration and exercises performed during RET sessions, a strong time and attention matched comparator group was selected; however, a no-treatment control group is not included. The Low-Dose group may lead to changes in depressive symptoms by serving as a distraction, increasing behavioral activation and/or creating opportunities for socialization (e.g., other gym users, study team members), though controlling these via Low-Dose provides the strongest possible comparator to test a standard High-Dose prescription against. Strict standardization of the RET sessions and team interactions will be used to minimize this limitation. Further, the extent to which participants will be blinded to group remains unclear. While the PI, unblinded statistician, and outcome assessors will be masked, participants may identify their group based on the prescribed workload. As such, attempts will be made to keep the study hypothesis unknown to participants with a formal assessment of participant group preferences and guess of study hypothesis base. Even with these limitations, key strengths, including a large sample size, robust investigation of mechanisms, both clinician and self-report measures of depression, and inclusion of short and long-term follow-ups, substantially builds on

previous work and allows for rigorous testing of the utility of progressive, High-Dose RET for treatment of MDD.

Trial status

Protocol version data: October 1, 2024.
Date recruitment began: January 01, 2024.
Date recruitment completed: Anticipated June 01, 2028.

Abbreviations

MDD	Major depressive disorder
RET	Resistance Exercise Training
IRB	Institutional Review Board
DSMB	Data Safety Monitoring Board

Authors' contributions {31b}

JDM conceived of the study. All authors contributed to the development of the study design. PL (unblinded) and TAM (blinded) will oversee statistical analysis. JDM, SK, JEL, JMG, SLP, AM, SLC, SBG, JNB, and NGW will implement the present study. JDM, NGW, PL, ALP, WKL, SBG, JNB, and MH are named investigators for the project funding. JDM, JEL, JMG prepared the original draft of this manuscript. All authors contributed to the drafting of the protocol and this manuscript and approved of the final draft, and all authors will subsequently be included on the primary paper with opportunities for authorship on other secondary outcome papers if desired.

Funding {4}

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Data availability {29}

Deidentified data will be uploaded to NIMH Data Archives at regular intervals throughout the study duration and accessible to others. For access to data within the team, the primary analysis will be conducted by the trial statistician. Other members of the research team will also have access to data to perform any required analysis per the publication policy and perform secondary analyses.

Declarations

Ethics approval and consent to participate {24}

This protocol and the informed consent forms found on ClinicalTrials.gov have been reviewed and approved by the IRB to ensure compliance with applicable research and human participants rules and regulations.

Consent for publication {32}

Published results will not include individual participant information. Consenting processes are detailed above, and, upon reasonable request, a copy of the informed consent document and study materials are available from the corresponding author.

Competing interests {28}

The authors declare that they have no competing interests to disclose.

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