

Suicide Reduction in Schizophrenia via Exercise (SUnRISE): Study Protocol for A Multi-Site, Single-Blind, Randomized Clinical Trial of Aerobic Exercise for Suicide Risk Reduction in Individuals With Schizophrenia

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Study protocol

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Abstract

Background: Suicide risk among individuals with schizophrenia (SZ) is intractably high, with over 40% of individuals attempting to take their own lives during their lifetime and an estimated 5-10% completing suicide. At present, available pharmacological and psychotherapeutic treatments offer limited risk reduction benefits, thus there remain an urgent need to explore novel interventions that will ameliorate this risk. Aerobic exercise (AE) has been shown to improve a number of predictors of suicide risk (e.g., depressed mood, sleeping difficulties). As individuals with SZ display a highly sedentary lifestyle, AE may reduce suicide risk.

Methods: Employing a multi-site, single-blind, randomized clinical trial design, we will examine the impact of AE on risk for suicide and related variables in individuals with SZ. Participants will be randomized to one of two 12-week exercise interventions: AE or a stretching and toning (ST) control intervention. Primary outcome measures will include suicide risk (Columbia Suicide Severity Rating Scale, C-SSRS) and aerobic fitness (VO_2 max), along with additional measures of suicide risk, mood, emotion regulation, sleep, cognition, and physical activity, with assessments completed at baseline and after 6- and 12-weeks of interventions.

Discussion: It is hypothesized that AE will reduce suicide risk among individuals with SZ. This study may offer support for a more efficacious treatment method for this population in addition to the pre-existing pharmacological and psychotherapeutic treatment regimens.

Trial Registration: Clinicaltrials.gov, NCT03270098. Registered September 1, 2017.

Background

People with schizophrenia (SZ) are at an increased risk for suicide, with approximately 40–50% of individuals attempting to take their own lives during their lifetime and an estimated 5–10% completing suicide (1–3). Furthermore, suicide attempts among individuals with SZ are often more violent and lethal compared to individuals without a diagnosis, suggesting a higher intent to die (4). This highly elevated risk represents a serious public health concern and an important target for interventions.

Treatment approaches aiming to diminish suicide risk in individuals with SZ have centered primarily on pharmacotherapy and psychotherapy. Available pharmacological treatments have been found to offer only limited benefits to ameliorate these risks (5, 6). Clozapine has demonstrated some effectiveness in reducing suicidal behavior in patients with SZ (7), with other atypical antipsychotics have been found to be promising, but more evidence is needed (8). Similarly, evidence for the efficacy of psychotherapy is limited - a small RCT comparing cognitive behavioral therapy for suicide (CBTs; n = 25) vs. treatment-as-usual (n = 24) among individuals with psychosis found the CBTs group improved on primary outcome measures of suicidal ideation, and on secondary outcomes of hopelessness related to suicide probability, depression, psychotic symptoms, and self-esteem (9). However, systematic analyses focusing on the

benefits of psychotherapy on suicide risk in SZ are lacking (10). Thus, there remains an urgent unmet need to identify novel approaches to reduce suicide risk in people with SZ.

A number of risk factors have been identified as significant predictors of completed suicide among individuals with SZ including depressive mood, sleep difficulties, poor cognition, more severe positive and negative symptoms, as well as number of previous hospitalizations (11–15). Additionally, a recent review and meta-analysis has implicated a number of factors related to increased suicide risk in SZ including hopelessness, physical comorbidity, substance use, poor medication adherence, family history of psychiatric illness, as well as a higher intelligence quotient (15).

Consistent with these findings, sedentary behavior is highly prevalent in people with SZ, with rates far exceeding those in the general population (16). Studies in SZ have consistently shown sedentary behavior, lower physical activity and cardiovascular fitness, compared to non-clinical populations (17–19). Using actigraph measurements, our group has found individuals with SZ spend 81% of their wake time sedentary, which was significantly inversely correlated with aerobic fitness (AF), consistent with previous reports (20–22). Similarly, Strassnig et al. found that 98% of SZ subjects in their study ($n = 117$) displayed low age-adjusted AF (23).

A recent meta-analysis of 14 studies ($n = 80,856$ individuals) indicated a significant inverse association between physical activity and suicidal ideation (24). Additionally, a number of meta-analyses indicate that SZ patients engage in lower levels of physical activity than healthy controls, which is subsequently significantly associated with a number of predictors of suicide risk including depressed mood and more severe cognitive symptoms (22, 25–27). However, at present there are no studies examining directly the impact of AE on suicide risk in individuals with SZ.

Recent reviews and meta-analyses indicate AE training is effective in increasing AF in individuals with SZ, with VO_2 max-indexed improvements ranging from 8–38% (17, 25, 28–30). In our pilot RCT, subjects undergoing a 12-week, 3x/week, 1-hour AE training program improved their VO_2 max scores by 3.82 mL/kg/min (SD = 3.21), an 18% improvement, vs. a minimal change in the “treatment-as-usual” control group ($M = -.48$, SD = 3.07; -0.5% ; $F = 12.24$, $p = .002$; $n = 26$), indicating a large effect size (Cohen’s $d = 1.06$) (31, 32).

Examination of the putative neurobiology underlying suicide, select neurotrophins and inflammation markers show potential association with suicide risk, particularly Brain Derived Neurotrophic Factor (BDNF) – a meta-analysis of 16 studies indicated lower serum BDNF levels in SZ vs. healthy controls), including in drug-naïve patients (33). Similarly, a review by Buckley et al. found 9 of 11 SZ studies reported reduced serum BDNF vs. controls (34). These reductions appear to impact multiple brain regions including the dorsolateral prefrontal cortex, anterior cingulate, as well as the inferior and superior temporal gyrus (35). Studies assessing individuals who have previously attempted suicide indicate both lower levels of serum and plasma BDNF compared to non-attempters (36–39). However, a few studies have demonstrated no difference in serum BDNF levels between suicide attempters versus non-

attempters, nor correlations between plasma BDNF and clinical symptoms (40–43). To date, the only study that examined BDNF and suicidality in SZ found no difference in serum BDNF levels between suicide attempters and non-attempters (44). However, available studies have a number of limitations including use of clinical indicators of suicide rather than research measures and extended latency between evaluations of suicide risk and biomarkers. Additionally, few studies examined the longitudinal links between BDNF and suicide risk in individuals with SZ using parallel assessments. Given previous literature has suggested BDNF as a potential biomarker for suicide risk, further research is necessary to elucidate the role of BDNF and suicide risk in SZ.

In summary, there remains an urgent unmet need to identify novel approaches to target suicide risk in people with SZ. Converging lines of animal, basic human and clinical research support the scientific premise for this project, suggesting AE, a novel intervention, may potentially ameliorate suicide risk in people with SZ. This study takes advantage of the infrastructure of a large, ongoing NIMH R01-funded project investigating the effects of AE on cognition in individuals with SZ. The relatively large size of the study cohort (n = 160) would permit examination of the impact of multiple covariates and biomarkers, as well as intervention characteristics. Such knowledge will inform development of more granular and precise models of the mechanisms underlying suicide risk in this population.

STUDY AIMS

The aim of this study is to examine the impact of AE training on suicide risk and related predictors in individuals with SZ.

Hypothesis 1.1

At 12-weeks, subjects in the AE training will significantly reduce their suicide risk compared to controls.

Hypothesis 1.2

Increases in aerobic fitness will predict reduction in suicide risk.

Hypothesis 2.1

At 12-weeks, subjects in the AE training will significantly improve their depressed mood, sleep quality and quantity, and executive functioning compared to controls.

Hypothesis 2.2

AE-induced improvements in suicide risk from baseline to 6 weeks to 12 weeks will be mediated by decreases in depressed mood and improvement in sleep quality and quantity, and executive functioning.

Methods/design

This is a multisite, single-blind, randomized clinical trial testing an intervention to improve suicide risk in individuals with psychosis. The Consolidated Standards of Reporting Trials (CONSORT) guidelines will be followed to ensure the standardized conduct and reporting of research. This protocol has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The checklist is presented in Additional file 1. Details regarding the study procedure are outlined in Figure 1. Amendments to the current protocol will be reported to the IRBs, trial participants, and The Trial Journal.

The interventions and data collection will take place at four geographically diverse sites in the United States: Icahn School of Medicine at Mount Sinai (New York), University of North Carolina at Chapel Hill (North Carolina), Augusta University (Georgia), and Stanford University (California). Each site has access to an exercise facility and spaces dedicated for blood drawing, biological samples analyses and banking, and VO₂max assessments.

Recruitment of 160 eligible participants will be conducted independently across the four sites. Each site PI will contact clinicians in their healthcare systems and local communities and inform them about the study so that they may inform their eligible patients of the study. Brochures will be left at various relevant outpatient facilities. Interested individuals may speak with a member of the research team who will describe the study in more detail and will invite them to enroll. A short screening interview will be conducted by a researcher remotely by phone to ensure that participants satisfy inclusion criteria.

The number of screens, eligible subjects, and reasons for non-participation will be tracked using the CONSORT guidelines. In an earlier pilot study, a similar procedure was employed with 77% of approached individuals recruited. Refusals were related primarily to logistical/physical health reasons. Subjects' retention was high, with only 1/16 AE subjects discontinuing due to AE program dislike. In the ongoing parent R01-funded protocol, to date 71% of approached individuals consented to participate in the study. Formal recruitment for the parent study began in May of 2018. Formal recruitment for this amended study began in November of 2019.

Eligibility Criteria

Inclusion Criteria: 18-55 years of age; DSM-V diagnoses of SZ, schizoaffective disorder, or schizophreniform disorder; taking an antipsychotic medication for at least 8 weeks and on current dose for 4 weeks and/or taking an injectable depot antipsychotic with no change in last 3 months; medically cleared by a physician to take part in VO₂max tests and AE/ST training; capacity to understand all the potential risks and benefits of the study; and consented to participate in the parent R01 study ("Improving Cognition via Exercise in Schizophrenia"; MH110623; PIs: Kimhy & Stroup) which aims to assess the impact of AE on cognitive and daily functioning in people with SZ.

Exclusion Criteria: DSM-IV diagnosis of alcohol/substance abuse (except nicotine) within the last month or a diagnosis of alcohol/substance dependence (except nicotine) within the last 6 months; initiation of anti-depressants, mood stabilizers, or other medications known to impact cognition in previous 4 weeks

or any changes in doses during this period; history of seizures/head trauma with loss of consciousness (>10 min) resulting in cognitive sequelae; significant clinical abnormalities in physical examination, lab assessments, or ECG; neurological/medical conditions that could interfere with study participation (e.g. AIDS, unstable cardiac disease, stuttering); $BMI \geq 40$; untreated hyper- or hypothyroidism; pregnant/nursing; serious homicidal risk (past 6 months); “moderate” or more severe conceptual disorganization ($PANSS \geq 4$); poor English reading ability ($WTAR < 7$); and participation in a study with cognitive assessment in the past 3 months.

This study has been approved by the institutional review board of the Icahn School of Medicine at Mount Sinai, New York, New York; University of North Carolina, Chapel Hill, North Carolina; Stanford University, Stanford, California; and Augusta University, Augusta, Georgia. As part of the informed consent process, the rationale of the study and its methods will be described in detail and all questions will be answered. All participants will be asked to provide written informed consent before participation.

BASELINE MEASURES

Baseline assessments follow an initial phone screen and occur over the course of 3 visits. Primary outcome measures of the current study are assessed via administration of The Columbia Suicide Severity Rating Scale (C-SSRS) by a blinded, trained rater. Four additional measures of suicidality supplement the C-SSRS: InterSePT Scale for Suicidal Thinking, Beck Suicide Ideation Scale, Beck Hopelessness Scale, and Reasons for Living Inventory.

In accordance with the parent study protocol, secondary measures will also be collected at this time. Descriptive data will include gender, age, ethnic and racial background, employment status, education level, current living arrangements, current medications, menstrual cycle information (if applicable), and contact information for the participant’s primary mental health care provider. Several questionnaires will be administered at this time including the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Childhood Trauma Questionnaire (CTQ), Pittsburgh Sleep Quality Index (PSQI), Fagerström Test for Nicotine Dependence (FTND), International Physical Activity Questionnaire (IPAQ), Toronto Alexithymia Scale (TAS-20), Emotion Regulation Questionnaire (ERQ), and The Satisfaction with Life Scale (SLS). The Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) will be administered by a trained clinician to confirm diagnoses of psychiatric illnesses. Severity of psychotic symptoms will be assessed using the Positive and Negative Syndrome Scale (PANSS). A medical physician associated with the study at each site will collect a medical history and conduct a medical examination. A urine Toxicology Screen and a pregnancy test (if applicable) will be taken along with blood samples. Aerobic fitness as indexed by $VO_2\max$ will be assessed with the use of electro-magnetically braked cycle ergometers by a cardiologist associated with each site.

RANDOMIZATION

After signing informed consent and undergoing baseline assessment of primary and secondary outcome measures, eligible participants will be assigned 1:1 randomly via computer to one of two 12-week,

3x/week, 1-hour interventions: 1) aerobic exercise intervention (AE); or 2) a stretching and toning control intervention (ST). Participants will receive intervention assignment via secure telephone call.

BLINDING

While participants, exercise trainers, and coordinators cannot be blinded, the assessors of primary and secondary outcomes are blind to participants' allocations by the following procedures. Suicide risk as well as assessments of aerobic fitness, cognitive, and daily functioning will be conducted by blinded evaluators (cognitive raters and medical professionals). The raters and medical professionals are not involved in the allocation process or the exercise intervention. Before the outcome measurements begin, participants, coordinators, and exercise trainers are instructed not to reveal any information regarding the allocation or exercise intervention. Data from the pilot study for the parent R01 study indicates that the risk for un-blinding is minimal – only 2 of 41 subjects were un-blinded with no status disclosures during any of the cognitive tests, clinical and functioning interviews. In the ongoing parent R01-funded study, only one subject was unblinded to date, with no status disclosures during any of the cognitive tests, clinical and functioning interviews.

INTERVENTIONS

Patients assigned to AE or ST receive treatment as usual from their treatment providers. The interventions are conducted at local site-affiliated exercise facilities, held in small groups between 1 and 4 subjects, and led by a certified exercise trainer. A non-blinded member of the research team will be present during all exercise sessions to set-up and manage equipment (e.g. heart rate monitors), as well as record behavioral data. All subjects are encouraged to hydrate and take breaks as needed.

Both the AE and ST treatment groups will exercise for one hour three times a week. This frequency was chosen based on previous studies of AE in SZ and informed by federal and ACSM guidelines which recommend 150 min of moderate-intensity AE per week over 3 days (45,46). Such activities expend 3-5.9 times the energy expended at rest and are defined as activities in which the subject is able to talk while engaging in the activity. A group exercise format with a trainer was chosen over individual independent training based on findings indicating lower attrition rates in AE RCTs using trainers (25).

At the beginning of each AE session, the trainer will lead participants through a 10-minute warm-up period. The following AE portion of the session will consist of participants using AE equipment. Each site is equipped with identical equipment including a LifeSpan TR 1200i treadmill, LifeSpan S1 stationary bike, NordicTrack E7.5 Elliptical machine, and an Xbox video-game console with a Kinect motion sensing device that will run Your Shape Fitness Evolved 2012 (Ubisoft Inc., San Francisco, CA), an interactive whole-body fitness activity software. The Xbox Kinect was selected due to the American Heart Association recommendation of the console and similar equipment as tools for promoting physical activity. Previous studies demonstrated the device's capability of stimulating moderately-intense aerobic activity in adults, with significantly higher enjoyment ratings as compared to "traditional" exercises (47–49). Participants will be free to choose the equipment they use, with encouragement from the trainer to

change activities throughout the session to diversify physical exercise routines. Each session will end with a trainer-led 5-minute cool-down period.

Intensity of training in the AE condition will be individualized to each participant based on his/her maximal heart rate as determined during the VO_2 max test conducted at baseline. During Week 1, training will aim to maintain the participant's HR at 60% of their max HR. This goal will increase to 65% in Week 2, 70% in Week 3, and 75% for the remainder of the 12 weeks. HR will be monitored using Polar V800 HR monitors (a digital watch connected to a Bluetooth-enabled H10 sensor strap) that participants will wear during sessions (50). The monitors will be programmed to emit a soft beeping sound when the participant's HR drops below the individually-targeted weekly AE intensity level. In this case, the trainer will encourage him/her to achieve their target goal. At session's end, the data is up-loaded from the monitors to a computer and analyzed using Polar Flow Sync software.

The stretching and toning (ST) condition is designed to replicate the variables of the AE condition such as schedule, duration, facilities, format, trainer contact, social interactions, etc. without affecting aerobic fitness. Similarly to the AE training sessions, ST sessions will begin with a 10-minute warm-up period led by the trainer. The following 45-minutes of each session will consist of a mixture of static stretching positions, low-impact toning exercises, and yoga- and tai chi-inspired routines using the Xbox Kinect. ST exercises are recommended by American College of Sports Medicine (ACSM) guidelines to improve flexibility (45,46). To maintain interest, new exercises will be introduced every week. While static stretching may result in limited transient HR increases, it provides limited aerobic fitness benefits (51 – 54). Just as in the AE condition, each ST session will end with a trainer-led 5-minute cool-down period.

Intensity of training in the ST condition will also be individualized per participant based on his/her maximal heart rate as determined during the VO_2 max test conducted at baseline. However, the training will aim to keep the participant's HR below 60% of their max HR. HR will be monitored using Polar V800 HR monitors (a digital watch connected to a Bluetooth-enabled H10 sensor strap) that participants will wear during sessions (50). The monitors will be programmed to emit a soft beeping sound when the participant's HR exceeds the individually-calculated ST maximum intensity level. In this case, the trainer will encourage him/her to rest until his/her HR lowers adequately. At session's end, the data is uploaded from the monitors to a computer and analyzed using Polar Flow Sync software.

Training Fidelity

In both training conditions, training fidelity will be monitored and indexed by 1) the number of sessions attended; and 2) the number of minutes per session the participant trained with his/her HR above (for AE condition) or below (for ST condition) the designated training intensity. The in-session training intensity is included to address the possibility that participants may attend the sessions but exercise too lightly (for AE condition) or too intensely (for ST condition).

Training Safety

At the end of each week of training, potential minor and moderate exercise-related adverse events will be recorded (in addition to serious adverse events; SAE). These may include musculoskeletal/soft tissue (muscle soreness; muscle pull/strain; joint pain, falls), cardiovascular (fatigue; dyspnea; angina or chest pains that are resolved with rest), and skin-related side-effects (blisters; chafing). If cases chest pain ensues, the medical physician and principal investigator associated with each site will be called to ensure the safety of the participant. Previous reports indicate the risk of adverse events as part of AE-related intervention studies is small (55). The screening procedure, the use of a “start low and go slow” strategy, the close monitoring of exercise intensity, and the presence of a certified exercise trainer will minimize the risk of SAE and adverse events.

OUTCOME MEASURES

All outcome measures will be identically assessed by the same examiners throughout a subject’s participation in the study. See Figure 2 for a full assessment schedule. The following procedures will be administered by trained clinical raters, research coordinators, and medical professionals adhering to standardized protocols.

Suicide Risk

Blinded Clinical Raters will administer suicide risk measures to all participants during baseline, 6-week, and 12-week research visits. As part of the protocol, the clinical raters will obtain certification in the administration of the suicide, clinical, and other measures prior to initiating the study, as well as annually. For assessments of suicide risk, all current and future raters will complete the certificate training for the C-SSRS. Additionally, Dr. Goodman, an expert on suicide risk, will be available for inquiries/supervision regarding assessment of suicide risk throughout the study duration.

The Columbia Suicide Severity Rating Scale (C-SSRS) will serve as a primary outcome measure of suicide risk (56). The C-SSRS is a 12-item, semi-structured interview that measures 4 suicide risk related domains: ideation severity, ideation intensity, behavior, and lethality. To address potential safety concerns associated with recruitment of individuals with higher suicide risk, all participants will also be administered the C-SSRS by phone at 3- and 9-weeks after baseline. Additional secondary measures of suicide risk will include The InterSePT Scale for Suicidal Thinking (ISST); The Beck Suicide Ideation Scale (BSIS); Beck Hopelessness Scale (BHS); and the Reasons for Living Inventory (RLF) (57–60). All the suicide risk measures will be administered at baseline, and after 6-, and 12-weeks in parallel to the assessments of the parent R01-funded protocol.

Secondary Measures

Data on demographics, medical history, and diagnoses will be obtained at baseline. Diagnoses will be established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) by a well-trained clinical rater. A medical doctor will conduct a full medical examination of each patient and take a

thorough medical history. Demographic information and additional clinical information will be collected by a member of the research team.

Data on medications, sleep, menstrual phase, and smoking will be collected at baseline, and after 6-, and 12-weeks by a member of the research team. Antipsychotic medications will be indexed by chlorpromazine equivalence. As other medications may impact outcomes, medication use/changes will be tracked using three broad classes: 1) antidepressants; 2) mood stabilizers; and 3) other medications. As indices allowing direct comparisons of medications are not available, for each class the use of relevant medications at baseline will be documented using a dummy variable (1, 0), along with increases, no change, decreases, or discontinuation at follow-ups (1, 0, -1, or -2, respectively). PRN use of medications that may impact cognition (e.g., antihistamines for allergies) during 48 hours prior to cognitive and AF tests will be assessed, and the tests will be postponed by 24 hrs. A similar strategy will be used to handle medications known to impact biomarkers (e.g., SSRIs on BDNF). Sleep during the 24 hours prior to cognitive and AF tests will be assessed using an abbreviated version of The Pittsburgh Sleep Quality Index (PSQI), a measure used extensively in SZ studies (61–63). If a subject reports substantial acute sleep loss that is likely to influence outcome (<4 hours sleep), the evaluations will be postponed until sleep is restored (64). Smoking frequency and dependence as well as the number of cigarettes smoked in the 4 hours prior to tests (nicotine half-life= \sim 2 hours) will be recorded using the Fagerström Test for Nicotine Dependence (FTND) (65–67).

Psychiatric Symptoms

Symptom severity will be assessed with the Positive and Negative Syndrome Scale (PANSS) along with The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). These assessments will be administered by blinded clinical raters at baseline, 6-weeks, and 12-weeks.

Cognitive Functioning

The composite score of the MATRICS Consensus Cognitive Battery (MCCB) will stand as the primary cognitive functioning assessment and will be administered by blinded clinical raters at baseline, 6-weeks, and 12-weeks. The WTAR will additionally be utilized at baseline to assess reading ability for eligibility.

Daily Functioning

The total score of the Specific Levels of Functioning scale (SLOF; informant version) will serve as the chief daily functioning outcome measure, along with The UCSD Performance-based Skills Assessment (UPSA) and the Schizophrenia Cognition Rating Scale (SCoRS). These measures of daily functioning will be administered by blinded clinical raters at baseline, 6-weeks, and 12-weeks.

Aerobic Fitness

Aerobic fitness will be determined according to participants' VO_2 max. The VO_2 max tests are completed by an exercise physiologist under the supervision of a physician using electro-magnetically braked cycle

ergometers at baseline, 6-weeks, and 12-weeks. A blinded cardiopulmonary physiology expert will review each test to assess for the quality of the test and to ensure that no medical issues arise that would prevent the participant to safely continue exercise.

Physical Activity

Data gathered by an accelerometer (wGT3x-BT) worn on the wrist of the non-dominant hand will provide a measure of objective physical activity (68). This measure will be performed at the baseline and 12-week follow-up visits. The participant will wear the device for seven consecutive days. Data will be sampled at a frequency of 80Hz for this duration. Established cut points will be used to determine physical activity (69). Self-reported physical activity will be assessed with the International Physical Activity Questionnaire (70).

Biospecimens

A urine sample will be collected by a member of the research team at baseline, 6-weeks, and 12-weeks to be used for toxicology screen (Alere iCup; 71). Blood samples will be collected by a certified phlebotomist. All samples will be collected between 9-10am to minimize potential diurnal-related variability. The samples will be analyzed for fasting Hemoglobin A1c and a lipid panel as well as several biomarkers of cognitive change including neurotrophins and inflammation. Assessment of neurotrophins and inflammation markers will include: serum BDNF (R&D Systems, Minneapolis, MN); Nerve Growth Factor - NGF Emax Immuno Assay Systems (Promega, Sunnyvale, CA); Neurotrophin-3 - NT-3 Emax Immuno Assay Systems (Promega, Sunnyvale, CA); Neurotrophin-4 - NT-4 DuoSet ELISA Development Kit (R&D System, Minneapolis, MN); Tumor Necrosis Factor alpha (TNF- α) - MILLIPLEX MAP Human High Sensitivity Immunology Multiplex Assay (Millipore, Billerica, MA); Interleukin-6 (IL6) - MILLIPLEX MAP Human High Sensitivity Immunology Multiplex Assay (Millipore, Billerica, MA); and C-Reactive Protein (CRP) - Cobas Integra 400 Plus (Roche Diagnostics, Indianapolis, IN).

Emotion Regulation, Trauma, and Quality of Life

Questionnaires will be administered by a member of the research team at baseline and 12-week follow-up to collect information regarding emotion regulation (ERQ), alexithymia (TAS-20), childhood trauma (CTQ; only administered at baseline), and the participant's satisfaction with their life (SWL).

SAFETY MEASUREMENTS/ADVERSE EVENTS

Exercise Safety Measures

At the end of each week of training, potential exercise-related minor and moderate adverse events will be recorded and monitored in addition to serious adverse events (SAE). These may include musculoskeletal/soft tissue (muscle soreness; muscle pull/strain; joint pain, falls), cardiovascular (fatigue; dyspnea; angina or chest pains that are resolved with rest), and skin-related side-effects (blisters; chafing). If chest pain ensues, the medical physician and principal investigator associated with each site

will be called to ensure the safety of the participant. Previous reports indicate the risk of adverse events as part of AE-related intervention studies is small (55). The screening procedure, the use of a “start low and go slow” strategy, the close monitoring of exercise intensity, and the presence of a certified exercise trainer will minimize the risk of SAE and adverse events.

Suicide Risk Safety

To address potential safety concerns associated with recruitment of individuals with higher suicide risk, all participants will also be administered a suicide risk assessment (i.e., C-SSRS) by phone at 3- and 9-weeks after baseline, in addition to the suicide risk assessments scheduled during research visits at baseline, 6-, and 12 weeks. All assessments will capture suicidal symptoms from the last administration of the instrument. The raters will consult with the site PI regarding the detection of any suicidality, including passive suicidality. Any subject with a C-SSRS score equal or greater than "4" (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) will require a consultation with Dr. Scott Stroup, the project's Medical Director, and Dr. Marianne Goodman, the project's suicide expert. Any subject that scores a "5" (Active Suicidal Ideation with Specific Plan and Intent) and judged to be actively suicidal, will require urgent clinical evaluation for the possibility of hospitalization, and he/she will be escorted to the closest ER by study staff. Dr. Goodman has extensive clinical experience treating veterans at high risk for suicide and is available by cell phone 24/7, should clinical consultation regarding study participants be necessary.

Data Monitoring

A NIMH-approved Data and Safety Monitoring Board (DSMB) was established in December of 2017 to oversee the parent study. The members of the DSMB have no financial, scientific, or other conflict of interest with the study and have no affiliations with any of the participating institutions. All materials, discussions and proceedings of the DSMB are completely confidential and objective. The DSMB will meet every 6 months, or as deemed necessary. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended by the principal investigators and members of his staff. All Serious Adverse Events (SAE) will be reported to the DSMB in addition to the IRB and NIMH.

Auditing

The current study is monitored by the NIMH Office of Clinical Research (OCR)'s Clinical Research Education, Support, and Training (CREST) program. (<https://www.nimh.nih.gov/funding/clinical-research/nimh-clinical-research-education-support-and-training-crest-program.shtml>). The CREST Program aims to establish accurate and verifiable clinical research study data, as well as compliance with Good Clinical Practice and human subjects safety regulations. As part of the program, NIMH staff conduct annual site visits. Additionally, the study is monitored by a Data and Safety Monitoring Board (DSMB) that meets twice annually during the duration of the study.

Sample Size Calculations

A power analysis was considered for determining sample size. However, a power analysis was ultimately determined not to be appropriate for the current trial due to the lack of direct data on the relationship between aerobic exercise and reduction in suicide risk. Additionally, recruitment and sample size for this protocol is associated with the ongoing parent R01-funded protocol.

The sample size for the parent R01-funded study is 200 outpatient individuals with SZ. This sample size was determined based on a focus on cognition as the primary outcome, specifically the MCCB total composite score. Prior literature suggests average scores of individuals with SZ fall between 1 and 2.5 standard deviations lower than MCCB averages. Therefore, a 0.50 standard deviation was chosen as a meaningful target effect size for powering the trial. The pilot for the parent study found a large effect size for the AE intervention group compared to controls suggesting a 0.893 standard deviation improvement in the intervention group compared to controls. The parent study sample size calculations assumed a loss-to-follow-up rate of 20% with 80 participants remaining in each arm (100×0.8). According to these calculations, the parent study is powered to detect moderate or larger effect size difference with >80% power. The current study retains confidence that the sample size will provide adequate power to detect a clinically meaningful effect size for suicide risk as the primary outcome.

Data Analyses

All primary analyses will be carried out on an intent-to-treat (ITT) basis, i.e. all subjects randomized will be analyzed according to the treatment they were assigned regardless of adherence to treatment. Level of fidelity to training intensity, accounting for adherence, will be controlled for in these analyses. All statistical tests will be two-sided with critical value $\alpha=5\%$.

Mixed effects regression will be used to model suicide risk as a function of time (0, 6, 12 weeks), treatment group (AE or ST), interaction of time by treatment group, and site (1, 2, 3, or 4). The efficacy of AE to improve suicide risk in people with SZ will be represented by the statistical significance of the time by treatment group interaction. The effect of AE on mood, sleep, and executive functions will be tested by conducting similar analyses, i.e. mixed effects regression across 0, 6, and 12 weeks.

Mediators in the relationship between AE and suicide risk will be identified by multi-step process. A mediation effect will be estimated by taking the expected value of the total effect of AE on changes in suicide risk and subtracting the effect when changes in mood, sleep, and executive functioning have been controlled. These mediation effects will be tested by fitting a Structural Equation Model (SEM) with change in depressed mood, sleep and executive function from baseline to 6 weeks as mediators of the relationship between AE treatment and change in suicide risk from baseline to 6 weeks as well as later changes in suicide risk from 6 to 12 weeks using MPlus version 8. The mediator-outcome relationship can be confounded by other time varying covariates (e.g. BMI changes) and these will also be adjusted for in the model.

Change in suicide risk from baseline will be modeled using mixed effect regression predicted by contemporaneous change in aerobic fitness from baseline as measured by VO₂max tests (at 6 and 12 weeks), controlling for treatment group and other covariates. The ability of aerobic fitness improvement to predict reduction in suicide risk will be represented by a statistically significant positive regression coefficient for change in aerobic fitness.

Demographic and other biologically relevant baseline variables (e.g. sex, depression, smoking status, etc.) will be included as control variables if there is evidence of randomization imbalance in them. Multiple imputation will be used to handle missing data using the MI and MIANALYZE SAS procedures.

Confidentiality & Data Management

All study documents will be deidentified and labeled using participant identification codes. The identification code key, contact information, consent forms, and medical documents with personal health information will be kept confidential. Hard copies are kept in secure, locked cabinets. Electronic copies will be stored in password-protected computers. Only IRB authorized individuals will be able to access study data.

Discussion

Individuals with SZ are at an elevated risk for committing and completing suicide (1–3). Current pharmacological and psychotherapeutic treatment approaches provide limited benefits to ameliorate suicide risk in this population. Aerobic exercise may help mitigate many of the predictors of suicide risk. Therefore, engaging individuals with SZ in AE may be a beneficial treatment approach.

Trial Status

This trial (Protocol version 1.7, January 4, 2020) is currently active. Recruitment of participants for the parent study started in May of 2018. Recruitment for the Suicide Reduction in Schizophrenia via Exercise amendment started in November of 2019. Recruitment of participants is scheduled to be completed July 31, 2021.

Abbreviations

ACSM: American College of Sports Medicine

AE: Aerobic Exercise

AF: Aerobic Fitness

BAI: Beck Anxiety Index

BDI: Beck Depression Index

BDNF: Brain-derived Neurotrophic Factor

BHS: Beck Hopelessness Scale

BSS: Beck Suicide Ideation Scale

BMI: Body Mass Index

CBTs: Cognitive Behavioral Therapy for Suicide

C-SSRS: Columbia Suicide Severity Rating Scale

CTQ: Childhood Trauma Questionnaire

DSM: Diagnostic and Statistical Manual of Mental Disorders

DSMB: Data Safety and Monitoring Board

ERQ: Emotion Regulation Questionnaire

FTND: Fagerström Test for Nicotine Dependence

HR: Heart rate

ICE: Improving Cognition via Exercise

IPAQ: International Physical Activity Questionnaire

IRB: Institutional Review Board

ISST: The InterSePT Scale for Suicidal Thinking

ITT: Intent-to-treat

MCCB: MATRICS Consensus Cognitive Battery

NIMH: National Institute of Mental Health

PANSS: Positive and Negative Symptom Scale

PRN: Pro re nata (“as needed”)

PSQI: Pittsburgh Sleep Quality Index

RCT: Randomized Clinical Trial

RFL: Reasons for Living Inventory

SAE: Serious Adverse Event

SCID: Structured Clinical Interview for DSM-V Axis 1 Disorders

SCORS: Schizophrenia Cognition Rating Scale

SEM: Structural Equation Model

SLOF: Specific Levels of Functioning scale

SMI: Serious Mental Illness

SSRI: Serotonin Reuptake Inhibitors

ST: Stretching and Toning

SWL: Satisfaction with Life Questionnaire

SZ: Schizophrenia

TAS-20: Toronto Alexithymia Scale

UPSA: UCSD Performance-based Skills Assessment

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Mount Sinai School of Medicine IRB00000204. Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Availability of Data and Materials

We intend to publish this protocol, but at the this, we have no plans to provide the participant-level dataset. This study is funded by the National Institute of Health, so the dataset may be publicly available in the future. Statistical code may be provided upon request.

Competing interests

The authors declare that they have no competing interests.

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design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Authors' contributions

DK and TSS designed the study and acquired funding. MG, MW, LHO, JM, LFJ, JSB, MB and RS contributed to the development of the protocol. DK, TSS, MG, and LHO are responsible for project implementation. KBF and DK wrote the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

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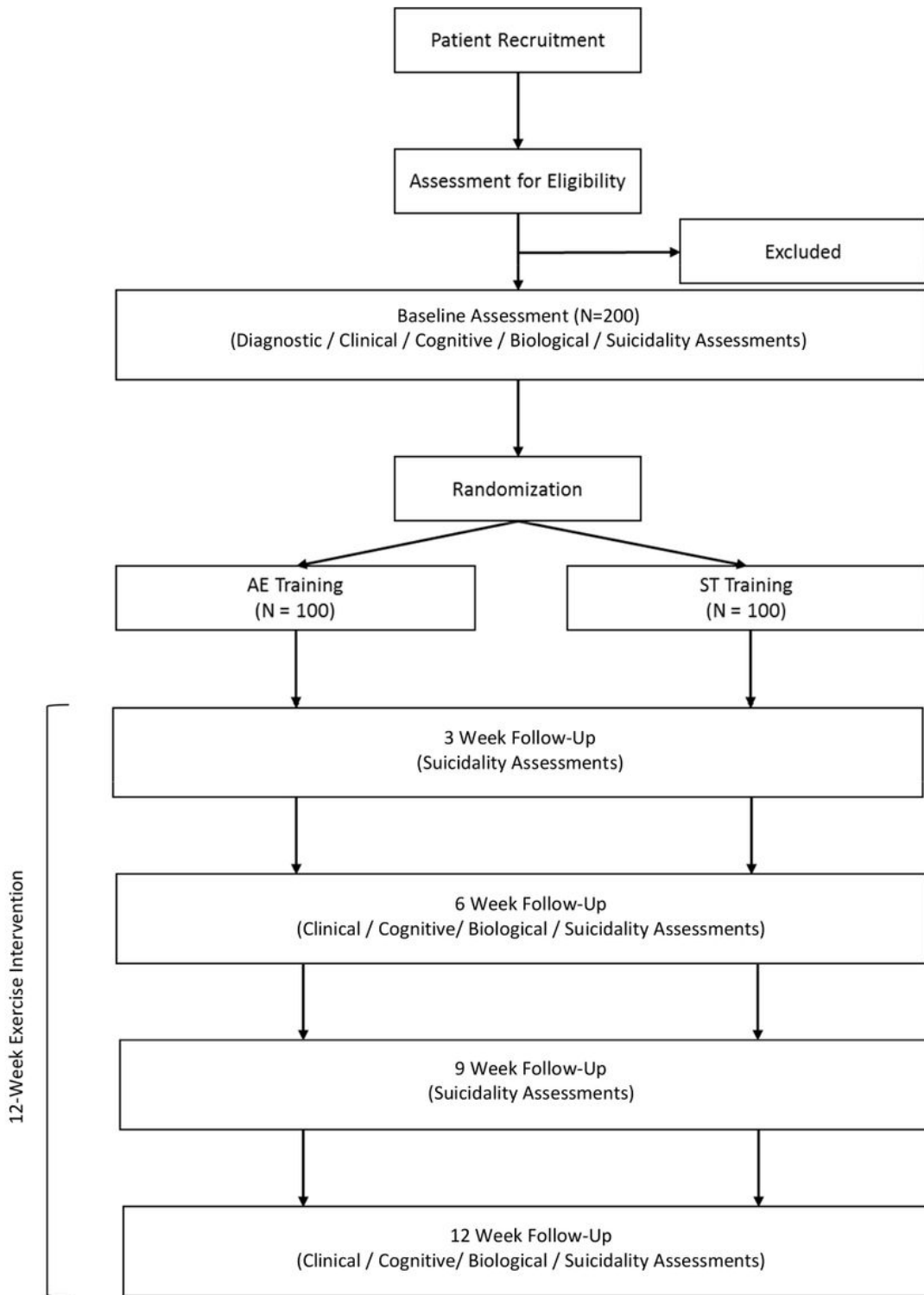
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Note: AE: Aerobic Exercise; ST: Stretching and Toning.

Figure 2

Study Protocol

Supplementary Files

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