University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

Version date: 08.15.2024

Principal Investigator: Dr. Alexandria Arickx, MD

Study Title: Low-Volume High Intensity Interval Training during Inpatient Stroke Rehabilitation: A Feasibility Trial.

Co- Investigator(s): Bria Bartsch OT. OTR/L., Dr. Sandra Billinger, PT. PhD., Dr. Ann Wingard, DO.

I. Purpose, Background and Rationale

A. Aim and Hypotheses

The objective of this study is to explore the safety and feasibility of conducting low-volume, high-intensity interval training (HIIT) on a total body recumbent stepper (TBRS) in persons with stroke in an inpatient rehabilitation setting. HIIT has emerged as a promising exercise therapy for patients with stroke, with work from the REACH laboratory and others, showing that HIIT leads to improvement in overall walking capacity and endurance.[1-5] Furthermore, in people with stroke, HIIT has been reported to improve aerobic fitness, increase muscle strength, and improve neuroplasticity, which are vital for functional recovery after stroke.[4, 6-9] Previous studies exploring HIIT in stroke have primarily used treadmills, focused on outcomes in functional gait, and included participants with higher walking abilities.[1, 5, 10, 11] Given that many individuals post-stroke, however, experience significant motor deficits, balance impairment, and reduced cardiovascular fitness, HIIT may be more accessible when conducted on a TBRS. The TBRS minimizes upright balance demand, offers adaptations for hemiparesis, and allows for exercise to be prescribed using peak power output, which accounts for motor ability [12]. Previous research conducted by Dr. Billinger has demonstrated that a single bout of low-volume, short-interval HIIT, performed on a TBRS is safe and feasible in individuals with chronic stroke. Research is required, however, to determine the safety and feasibility of low-volume, short-interval HIIT, performed on a TBRS, in inpatient rehabilitation. Given the nature of increased neuroplasticity during the subacute phase of stroke, compared to the chronic phase[13], implementing an accessible HIIT paradigm during inpatient rehabilitation may prove beneficial for optimizing stroke recovery. **Determining the safety and feasibility of a low-volume, short-interval HIIT program, conducted on the TBRS, is a logical and critical next step in investigating ways to optimize stroke recovery.**

This proposed study will explore the safety and feasibility of HIIT using a recumbent stepper during inpatient stroke rehabilitation. **We hypothesize that a single bout of low-volume, short-interval TBRS HIIT will be safe and feasible in patients with subacute stroke admitted to inpatient rehabilitation.**

We will recruit up to 25 patients admitted to The University of Kansas Acute Inpatient Rehabilitation Unit with subacute stroke, age 18-85 years, to perform a single bout of short-interval (60 seconds), low-volume (10 minutes) HIIT on the TBRS, in line with the protocol used in STUDY00146161 (NCT04673994).

Aim 1: Explore the safety of short-interval; low volume HIIT in stroke. Safety will be defined as the presence of no study-related cardiac or serious adverse events.[14] We hypothesize that low-volume, short-

interval, TBRS HIIT will be safe in individuals with subacute stroke while admitted to inpatient rehabilitation during HIIT **(H1a)** and within the 30 minutes following HIIT cessation **(H1b)**.

Aim 2: Explore the feasibility of short-interval, low-volume HIIT in stroke. Feasibility will be assessed by adherence to the exercise session, attainment of target heart rates, and acceptability of the exercise. At least 75% of participants will complete the entire 10-minute HIIT bout, **(H2a)** and ≥75% of participants will reach target heart rates (75%-85% max HR) during ≥75% of the high-intensity intervals **(H2b).** To examine acceptability, the valid and reliable 8-item Physical Activity Enjoyment Scale (PACES-8) will be used, where higher scores indicate greater exercise enjoyment **(H2c)**[15-19].

B. Background and Significance

Globally, stroke is the second leading cause of death, and third leading cause of death and disability combined, often resulting in significant impairments in physical function and quality of life.[20] Multiple randomized controlled trials have shown that exercise performed before and after stroke decrease the likelihood of having an initial stroke and subsequent strokes, respectively,[21, 22] and exercise-based rehabilitation is crucial for optimizing functional recovery and cardiovascular health post-stroke [4, 6, 10]. However, traditional approaches, such as treadmill training and overground walking at low and moderate intensities, may not effectively stimulate improvements in cardiovascular fitness and may not be inclusive of individuals with a wide range of cognitive and motor abilities post-stroke. Evidence by Billinger et al.,[23] has demonstrated that cardiorespiratory fitness is significantly reduced in individuals with stroke compared to age- and sex-matched peers, and reduced cardiorespiratory fitness is associated with an increased risk for overall mortality[24] and poor functional recovery.[25, 26] This is likely due to the fact that individuals with low cardiorespiratory fitness expend more energy during tasks performed at submaximal effort (i.e., activities of daily living, walking and community activities) when compared to age-matched peers.[27] This results in greater engagement of sedentary behaviors, further exacerbating deconditioning and functional decline. [27, 28] As such, a critical need exists for exercise protocols to be implemented which target cardiorespiratory fitness and recovery post-stroke.

More recently, two randomized controlled trials[5, 29] and a superiority trial [30] sought to compare treadmill-based HIIT to treadmill-based moderate-intensity continuous training[5, 30] or standard of care [29] in participants with late subacute to chronic stroke. Findings indicated that HIIT facilitated the greatest improvements in gait function and cardiorespiratory fitness, and no study-related serious adverse events occurred.[5, 29, 30] Given the promising findings observed with treadmill-based HIIT, implementing more accessible HIIT paradigms for individuals post-stroke may prove beneficial for improving cardiorespiratory fitness and functional recovery.

Recent (NCT04673994) and ongoing (NCT05936008) work from Dr. Billinger's laboratory has been focused on exploring the feasibility of HIIT, using the TBRS, in chronic stroke to provide a more accessible modality for HIIT training. We have previously demonstrated that a single bout of low-volume, short-interval, TBRS HIIT is safe and feasible in individuals with chronic stroke.[14] However, research is required to explore the safety and feasibility of TBRS HIIT in subacute stroke. As neuroplasticity is increased during the subacute phase of stroke recovery, and evidence suggests that HIIT may upregulate neurotrophic factors and corticospinal activity in stroke, [31, 32] HIIT performed during the subacute phase

may further optimize neuroplasticity and recovery while improving cardiorespiratory fitness. This study will provide critical insight into the safety and feasibility of a single session of recumbent stepper HIIT, laying the groundwork for potential future studies seeking to optimize inpatient rehabilitation outcomes for stroke recovery.

Preliminary Data from Dr. Billinger's Laboratory: Exercise post-stroke is complex and requires a well-coordinated, experienced, multi-disciplinary team. Our team has developed the essential infrastructure and processes required to perform rigorous exercise trials in adults with stroke. Dr. Billinger has built a stroke recovery trial unit, fully integrated with KU Medical Center's physician partners, and has published on the role of physician engagement in successful stroke recovery trials.[33]

Dr. Billinger has successfully filled and completed enrollment in:

- Two acute stroke studies (n = 38; and n = 15) under 1.5 years as part of her career development award, K01 HD067318 (2011-2016). Dr. Billinger's career development award supported her work in 39 publications.
- An internally funded pilot study in subacute stroke using an 8-week moderate intensity exercise intervention (n = 10) that demonstrated a significant improvement in aerobic fitness with no adverse events.
- Two stroke studies (n = 69; and n = 12) that were conducted on The University of Kansas Inpatient Rehabilitation Unit. Dr. Billinger has great rapport with the Medical Director of KU's Inpatient unit as well as the chair of the Physical Medicine and Rehabilitation department.
- A trial on the KUMC inpatient rehabilitation unit, which included 20 participants with stroke. Participants were tested after conducting their therapies on the Inpatient Rehabilitation Unit (similar to as proposed in this study).

II. Research Plan and Design

A. Study Objectives: The objective of this study is to explore the safety and feasibility of conducting low-volume, high-intensity interval training (HIIT) on a total body recumbent stepper (TBRS) in persons with stroke in an inpatient rehabilitation setting. The study aims are as follows:

Aim 1: Explore the safety of short-interval; low volume HIIT in stroke. Safety will be defined as the presence of no study-related cardiac or serious adverse events.[14] We hypothesize that low-volume, short-interval, TBRS HIIT will be safe in individuals with subacute stroke admitted inpatient rehabilitation during HIIT **(H1a)** and within the 30 minutes following HIIT cessation **(H1b)**.

Aim 2: Explore the feasibility of short-interval, low-volume HIIT in stroke. Feasibility will be assessed by adherence to the exercise session, attainment of target heart rates, and acceptability of the exercise. At least 75% of participants will complete the entire 10-minute HIIT bout, **(H2a)** and ≥75% of participants will reach target heart rates (75%-85% max HR) during ≥75% of the high-intensity intervals **(H2b).** To examine acceptability, the valid and reliable 8-item Physical Activity Enjoyment Scale (PACES-8) will be used, where higher scores indicate greater exercise enjoyment **(H2c)**[15-19].

B. Study Type and Design: We propose a feasibility study with up to 25 participants with subacute stroke (18-85 years of age) admitted to The University of Kansas Acute Inpatient Rehabilitation Unit. Participants will be asked to engage in two visits, both located on the acute inpatient rehabilitation unit.

Visit 1
Visit 1 will take approximately 1 hour to complete. The Total Body Recumbent Stepper (TBRS) Submaximal Exercise Test, which is valid and reliable in persons with stroke, will be used to assess cardiorespiratory fitness. Following completion of the TBRS Submaximal Exercise Test, participants will complete a HIIT familiarization bout. Details on visit 1 procedures can be found in Section E.

Visit 2
Visit 2 will take approximately 1 hour to complete. Participants will complete the single bout of low-volume, short-interval HIIT on the TBRS. Vitals will be monitored throughout the HIIT bout. Details on visit 2 can be found in Section E.

C. Sample size, statistical methods, and power calculation

1. We plan to recruit a sample of up to 25 participants. This sample size aligns with other feasibility trials examining HIIT in stroke.[14, 34]
2. Blinding: No blinding will be used.
3. Analytic and statistical methods to be used: Descriptive statistics will be used to report adverse events, participants who completed the entire HIIT bout, target heart rates achieved, and PACES-8 scores.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):
We intend to enroll up to 25 participants (18-85 years of age) with subacute stroke admitted to The University of Kansas Acute Inpatient Rehabilitation Unit. Inclusion and exclusion criteria are outlined in the table below.

Inclusion criteria	-Both sexes between the age of 18-85 years at time of consent -Ischemic or hemorrhagic stroke at consent. People with stroke and newly diagnosed cardiovascular complications had >50% prevalence of recurrent stroke at 5 years.[35] Index stroke or recurrent stroke on same side as index stroke will be allowed. -Exercise continuously for minimum of 30 watts for 3 minutes on the recumbent stepper to demonstrate ability to perform the exercise test or therapist confirmation/documentation of participant's ability to use the recumbent stepper.[36] -No aerobic exercise contraindications[37] or other safety/physical concerns during the submaximal exercise test determined by the therapy team or inpatient physicians. -Able to communicate with investigators, follow 2-step command & correctly answer consent comprehension questions

Exclusion criteria	- Implanted pacemaker or defibrillator limiting exercise performance -Reported pain that limits or interferes with activities of daily living and physical activity/exercise -Acute MI in the last 2 days -Ongoing unstable Angina -Active Endocarditis -Symptomatic Severe Aortic Stenosis -Decompensated HF -Acute PE, PI, or DVT -Acute Myocarditis or Pericarditis -Other significant neurologic, orthopedic, or peripheral vascular conditions that would limit exercise participation -Oxygen-dependent chronic obstructive pulmonary disease -Neurological disease (Multiple Sclerosis, Alzheimer's disease, Parkinson's disease) -Pregnancy

Withdrawal/Termination of exercise criteria: A participant may withdraw from the study at any time or be withdrawn from the study at the principal investigator's discretion if exercise is deemed unsafe for continuation.

E. Specific Methods and Techniques used throughout Study:

All data collected during the study will be stored on a secure university server database (i.e., REDCap®).

Participant Recruitment and Screening

Potential participants will be identified for the study by the following methods: 1) University of Kansas Health System healthcare practitioners notify the study team of a potentially eligible participant, and/or 2) Electronic Medical Record (EMR) screening by the study team. A screening of the EMR will be conducted to determine if participants meet preliminary criteria, as outlined in the inclusion/exclusion criteria (i.e., no additional neurologic disease, oxygen-dependent chronic obstructive pulmonary disease, etc.). Potential participants who meet the preliminary criteria will then be approached for interest in participation.

For individuals who wish to participate, a study team member will review the consent form and complete the consent comprehension questions with this individual. If the individual chooses to participate and provides written informed consent, consent will be documented in EPIC O2, physician clearance for participation will be obtained from a KU Physical Medicine and Rehabilitation physician, and the following will occur:

Basic demographic information such as date of birth, age, sex, gender, height, weight, and race/ethnicity will be collected and stored in REDCap®. We will also collect: participant address, contact methods (phone and/or email), and stroke information (i.e., date of stroke, type of stroke, location of stroke, etc.).

Visits 1 and 2 will be performed by trained personnel with experience administering exercise in stroke. Visits will occur ≥2 hours after meals, and participants will be asked to avoid caffeine for 4-6 hours prior.

Visit 1:

1. The American College of Sports Medicine cardiac risk screen will be completed, as done in STUDY00147598 to provide increased insight into cardiovascular health.

2. Participants will be fitted with a Polar heart rate monitor to continuously monitor heart rate throughout exercise, and a resting blood pressure will be taken.
    - Substep: As shown in the inclusion/exclusion criteria, participants must be able to exercise at 30 watts for 3 minutes on the TBRS to demonstrate their ability to perform the Total Body Recumbent Stepper (TBRS) Submaximal Exercise Test. If inpatient therapists have not previously confirmed or documented the participant's ability to use the TBRS, the participant will be asked to demonstrate an ability to step at 30 watts for 3 minutes on the TBRS. Following successful completion of this task, participants will be asked to rest to allow their heart rate to return to near resting values. If a participant is unable to complete this task, they will be deemed ineligible for the study.

3. Participants will complete the TBRS Submaximal Exercise Test[38] with oversight from a trained study team member, and as performed in protocols STUDY00146161 and STUDY00147598. Participants will be asked to step at a step rate of ~90-100 steps per minute until one of the following occurs: 1) 85% of age-predicted heart rate maximum (HR_{max}) is reached, 2) All four stages of the test are completed, or 3) Participant requests to stop. Each stage of the test is approximately 3 minutes in duration and consists of increasing resistance. We have previously employed the TBRS Submaximal Exercise Test in subacute stroke with success.[39]
    - As done in STUDY00147598, American College of Sports Medicine Guidelines will be used to guide test termination indications for submaximal exercise testing:
    - Absolute Indications:
        - Drop in systolic blood pressure of >10 mmHg, despite an increase in workload,
        - Moderate to severe angina
        - Central nervous system symptoms (i.e., ataxia, dizziness, or near syncope)
        - Signs of poor perfusion (cyanosis or pallor)
        - Any arrhythmia that interferes with normal maintenance of cardiac output during e xercise
        - Technical difficulties with equipment that interferes with testing or participant safe ty
        - The individual requests to stop
    - Relative Indications:
        - Increasing chest pain
        - Fatigue, shortness of breath, wheezing, leg cramps, or claudication

- Exaggerate hypertensive response (systolic blood pressure >250 mmHg or diastolic blood pressure >115 mmHg)

4. Blood pressure will be taken immediately following completion of the TBRS Submaximal Exercise Test, as done in STUDY00147598, and participants will be asked to subjectively evaluate exercise intensity using the Rating of Perceived Exertion.

5. The participant will rest to allow heart rate and blood pressure to return to near resting values.

6. A HIIT familiarization bout will be performed, as done in STUDY00146161.
   - The familiarization will last for no more than 10-minutes. Participants will perform 1-minute high-intensity intervals at ~70% peak power output (range: 65-95% peak power output), interspersed with 1-minute active recovery intervals at ~10% peak power output. An upper heart rate limit of 85% HR_{max} will be used to align with the upper heart rate limit used in our TBRS Submaximal Exercise Test.

7. Blood pressure will be obtained. To complete the session, the participant's blood pressure must be <180/100 mmHg, and heart rate must be below <100 beats per minute. As such, blood pressure recordings may be repeated as necessary.

8. The heart rate monitor will be removed from the participant.

Visit 2

1. Participants will be fitted with a Polar heart rate monitor, and resting vitals (heart rate and blood pressure) will be obtained.

2. Participants will perform a 1-minute warm-up at ~30% peak power output.

3. Participants will perform the HIIT bout:
   - 1-minute high-intensity intervals will be interspersed with 1-minute active recovery intervals for a total of 10 minutes. As used in STUDY00147598, high-intensity intervals will be prescribed at ~70% peak power output (range: 65-95% peak power output) with a target heart rate range of 75-85% HR_{max} or 60-89% heart rate reserve. The upper heart rate limit of 85% HR_{max} aligns with the upper heart rate limit used in the TBRS Submaximal Exercise Test. Active recovery intervals will be performed at ~10% peak power output.

4. Blood pressure will be taken immediately post-HIIT, and participants will perform a ~1-minute cool-down at ~20% peak power output. Participants will also be asked to subjectively evaluate the HIIT bout using the Rating of Perceived Exertion.

5. Heart rate will be monitored 30minutes to one hour following HIIT completion and blood pressure will be recorded within one hour of conclusion of the study.

6. During the monitoring period, the PACES-8 will be administered to assess exercise acceptability.

7. The heart rate monitor will be removed from the participant.

F. **Risk/benefit assessment:**

Potential Benefits of Proposed Research

The participant may or may not benefit from this study. Researchers hope that the information gained from this study may be useful in developing increased insight into accessible HIIT modalities for stroke recovery during inpatient rehabilitation.

Potential Risks of Proposed Research

Exercise: There are certain risks and discomforts that may be associated with exercise such as temporary shortness of breath, muscle fatigue, sweating, and physical discomfort. It is extremely unlikely, but there is always the risk of having a serious heart problem, such as developing an abnormal rhythm, heart attack, or having another stroke during exercise. To protect and minimize risks during exercises, the study team will monitor heart rate and blood pressure during all exercise procedures and obtain physician clearance prior to exercise engagement. If a participant would report chest discomfort, dizziness or any other problems, exercise will be discontinued. We have successfully studied individuals with stroke during the TBRS submaximal exercise test (HSC#2173) during inpatient stroke rehabilitation without serious adverse events. We have also successfully implemented a single bout of low-volume, short-interval HIIT in chronic stroke (STUDY00146161). Our laboratory team is well equipped and trained to execute this study.

Blood pressure: A participant may experience mild discomfort in the upper extremity when assessing blood pressure due to cuff inflation. Should this occur, the cuff can be deflated.

Possibility of unknown risks: There may be other side effects or risks that are not yet known. The study team will work to minimize any discomfort associated with the aforementioned procedures.

G. Location where study will be performed: This study will take place at Kansas University Medical Center Inpatient Rehabilitation. Address: The Second Floor of 3910 Rainbow Blvd, Kansas City, KS 66103

H. Personnel who will conduct the study, including:

Members of the study team added to the IRB will be involved in determining participant eligibility, obtaining informed consent, providing ongoing information updates to the IRB, conducting study visits, and managing study data. Team members who are involved in the study will be trained on their respective duties and tested for competency prior to performing any tasks with participants. The principal investigator, Dr. Arickx, will oversee all study procedures to ensure compliance.

I. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

The REDCap® web-based system will be used for data entry, data monitoring, and linking participant ID to participant name. The consent forms and all paper copies will be kept in a locked filing cabinet in the REACH Lab in accordance with professional standards of privileged

information. Confidentiality is strictly safeguarded by HIPAA-compliant standards. Data from testing may also be stored on a spreadsheet using the unique subject code and stored on a secure network drive (P drive) with access only provided to the study team.

Adverse events will be assessed during each visit. Adverse event inquiries will end at the completion of the second visit. Any adverse event that occurs will be immediately reported to the PI(s) and then to the Human Subjects Committee per KUMC Human Subject Committee reporting policies. Dr. Arickx will be notified immediately of all grade 3 adverse events and any grade 2 or above cardiac adverse events. Should a participant experience an adverse event in any category rated 4 or greater according to CTCAE v5.0, that individual will be removed from the study. If more than 6 participants experience an adverse event in any category rated 3 or greater according to CTCAE v5.0, the study will be reviewed in conjunction with the Human Subjects Committee for possible termination.

Dr. McCasey Smith will serve as the internal safety monitor and receive quarterly reports on any adverse events.

III. Subject Participation

A. Recruitment and Informed consent process and timing of obtaining of consent:
Potential participants admitted to the University of Kansas Acute Inpatient Rehabilitation Unit will be identified for the study by the following methods: 1) University of Kansas Health System healthcare practitioners notify the study team of a potentially eligible participant, and/or 2) Electronic Medical Record (EMR) screening by the study team. A screening of the EMR will be conducted to determine if participants meet preliminary criteria, as outlined in the inclusion/exclusion criteria (i.e., no additional neurologic disease, oxygen-dependent chronic obstructive pulmonary disease, etc.).

Potential participants who meet the preliminary criteria will then be approached for interest in participation. For individuals who wish to participate, a study team member, trained on the informed consent process, will review the consent form, and complete the consent comprehension questions with this individual. Potential participants will be reminded that research is voluntary, and all questions asked will be answered by the trained study team member. We will make clear that their participation or lack thereof will not influence any care that may be received at KU Medical Center. Participants will be provided with a copy of their signed informed consent form, and we will electronically document that the participant consented to be in the study in EPIC O2.

Should a team member have any concern about a potential participant's ability to provide informed consent, they will refer to the principal investigator before obtaining informed consent.

B. Screening Interview/questionnaire: As outlined in Section E, preliminary screening will be performed using the EMR. Following EMR screening, and as necessary, a study team member will confirm inclusion/exclusion criteria verbally with the participant. Questions regarding eligibility may be directed to the participant's physician as well, as necessary.

C. **Alternatives to Participation:** The alternative to participating is not participating. Participants will be informed that this has no effect on the care that they receive at KU Medical Center, and participation is completely voluntary.

D. **Costs to Subjects:** This will be no monetary cost to the participant.

E. **How new information will be conveyed to the study subject and how it will be documented:** Aside from any new information that arises regarding risks associated with the study, no new information will be conveyed to the participant. If this occurs, they may be asked to sign a new consent form.

F. **Payment to participants:** Participants will receive $50 upon completion of the study.

G. **Payment for a research-related injury:** The following text will be included in the consent form: "Despite all safety measures, you might develop medical problems from participating in this study. You must report any suspected illness or injury to the study team immediately. If such problems occur, you will be provided with emergency medical treatment and the investigator will assist you in getting proper follow-up medical treatment. The investigator will not provide compensation for research-related injuries. Payment of lost wages, disability or discomfort is not available. You do not give up any of your rights by signing this form."

H. **Photo and Video Consent:** Participants may be photographed and or recorded during the two visits. These images and or videos may be used for presentation purposes.

IV. Data Collection and Protection

A. **Data Management and Security/Procedures to protect subject confidentiality:** As mentioned previously and as used in STUDY00146161 and STUDY00147598, the REDCap® web-based system will be used for data entry and data monitoring. Each participant will be assigned a unique participant ID, and REDCap® will be used to link participant ID to participant name. The informed consent forms will be kept in a locked filing cabinet in the REACH Lab in accordance with professional standards of privileged information. Confidentiality is strictly safeguarded by HIPAA-compliant standards. Data may also be stored on a spreadsheet using the unique subject code and stored on a secure network drive (P drive) with roll-based access only provided to the study team.

B. **Sample/Specimen Collection:** N/A

C. **Tissue Banking Collection:** N/A

D. **Procedures to protect subject confidentiality:** Study procedures to protect participant confidentiality are outlined above in sections II.I. and IV.A.

E. Quality Assurance / Monitoring: Study team members involved in the data collection process will be trained on their respective duties and tested for competency prior to performing any of these tasks with participants. Dr. Arickx will review the obtained data and collect self-audits as necessary to ensure quality of data collection.

V. Data Analysis and Reporting

A. Statistical and Data Analysis: Descriptive statistics will be used to report adverse events, participants who completed the entire HIIT bout, target heart rates achieved, and PACES-8 scores.

B. Outcome: We expect that a single bout of low-volume, short-interval HIIT will be safe and feasible in individuals with subacute stroke admitted to inpatient rehabilitation.

C. Publication Plan: We plan to publish findings from this study in a peer-reviewed journal. Findings may also be presented at conferences.

Bibliography

1. Gjellesvik, T.I., et al., *Effects of High-Intensity Interval Training After Stroke (The HIIT Stroke Study) on Physical and Cognitive Function: A Multicenter Randomized Controlled Trial.* Arch Phys Med Rehabil, 2021. **102**(9): p. 1683-1691.
2. Boyne, P., et al., *Moderate to Vigorous Intensity Locomotor Training After Stroke: A Systematic Review and Meta-analysis of Mean Effects and Response Variability.* J Neurol Phys Ther, 2024. **48**(1): p. 15-26.
3. Marzolini, S., et al., *Outcomes in people after stroke attending an adapted cardiac rehabilitation exercise program: does time from stroke make a difference?* J Stroke Cerebrovasc Dis, 2014. **23**(6): p. 1648-56.
4. Crozier, J., et al., *High-Intensity Interval Training After Stroke: An Opportunity to Promote Functional Recovery, Cardiovascular Health, and Neuroplasticity.* Neurorehabil Neural Repair, 2018. **32**(6-7): p. 543-556.
5. Boyne, P., et al., *Optimal Intensity and Duration of Walking Rehabilitation in Patients With Chronic Stroke: A Randomized Clinical Trial.* JAMA Neurol, 2023. **80**(4): p. 342-351.
6. Billinger, S.A., et al., *Aerobic exercise in subacute stroke improves cardiovascular health and physical performance.* J Neurol Phys Ther, 2012. **36**(4): p. 159-65.
7. Mattlage, A.E., et al., *Submaximal and peak cardiorespiratory response after moderate-high intensity exercise training in subacute stroke.* Cardiopulm Phys Ther J, 2013. **24**(3): p. 14-20.
8. Whitaker, A.A., et al., *Secondary Analysis of Walking Activities during the Acute Stroke Hospital Stay and Cerebrovascular Health.* Cardiopulm Phys Ther J, 2022. **33**(3): p. 130-137.
9. Whitaker, A.A., et al., *Lower middle cerebral artery blood velocity during low-volume high-intensity interval exercise in chronic stroke.* J Cereb Blood Flow Metab, 2023: p. 271678X231201472.
10. Gjellesvik, T.I., et al., *Effect of high aerobic intensity interval treadmill walking in people with chronic stroke: a pilot study with one year follow-up.* Top Stroke Rehabil, 2012. **19**(4): p. 353-60.
11. Boyne, P., et al., *High-Intensity Interval Training and Moderate-Intensity Continuous Training in Ambulatory Chronic Stroke: Feasibility Study.* Phys Ther, 2016. **96**(10): p. 1533-1544.
12. Crozier, J., Roig, M., Eng, J.J., MacKay-Lyons, M., Fung, J., Ploughman, M., Bailey, D.M., Sweet, S.N., Giacomantonio, N., Thiel, A., Trivino, M., Tang, A., *High-intensity interval training after stroke: An opportunity to promote functional recovery, cardiovascular health, and neuroplasticity.* Neurorehabil Neural Repair, 2018. **32**(6-7): p. 543-556.
13. Dromerick, A.W., et al., *Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans.* Proc Natl Acad Sci U S A, 2021. **118**(39).
14. Bartsch, B.L., et al., *Feasibility of a Recumbent Stepper for Short-Interval, Low-Volume High-Intensity Interval Exercise in Stroke.* J Neurol Phys Ther, 2024.
15. Huffman, M.K., et al., *Questions to Measure Enjoyment of and Satisfaction With Physical Activity: Are They Appropriate for Use in an Older Population?* Innov Aging, 2021. **5**(4): p. igab041.

16. Sari, Y.M., et al., *A Telehealth Home-Based Exercise Program for Community-Dwelling Older People with Dementia in Indonesia: A Feasibility Study.* Int J Environ Res Public Health, 2023. **20**(4).
17. Teques, P., et al., *Validation and adaptation of the Physical Activity Enjoyment Scale (PACES) in fitness group exercisers.* J Sport Health Sci, 2020. **9**(4): p. 352-357.
18. Chung, P.K. and K.M. Leung, *Psychometric Properties of Eight-Item Physical Activity Enjoyment Scale in a Chinese Population.* J Aging Phys Act, 2018: p. 1-6.
19. Brooker, P.G., et al., *The feasibility and acceptability of morning versus evening exercise for overweight and obese adults: A randomized controlled trial.* Contemp Clin Trials Commun, 2019. **14**: p. 100320.
20. Collaborators, G.B.D.S., *Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.* Lancet Neurol, 2021. **20**(10): p. 795-820.
21. Cowan, L.T., et al., *Changes in physical activity and risk of ischemic stroke: The ARIC study.* Int J Stroke, 2023. **18**(2): p. 173-179.
22. Turan, T.N., et al., *Relationship between risk factor control and vascular events in the SAMMPRIS trial.* Neurology, 2017. **88**(4): p. 379-385.
23. Billinger, S.A., J.M. Taylor, and B.M. Quaney, *Cardiopulmonary response to exercise testing in people with chronic stroke: a retrospective study.* Stroke Res Treat, 2012. **2012**: p. 987637.
24. Kaminsky, L.A., et al., *2023 update: The importance of cardiorespiratory fitness in the United States.* Prog Cardiovasc Dis, 2024.
25. Mackay-Lyons, M.J. and L. Makrides, *Exercise capacity early after stroke.* Arch Phys Med Rehabil, 2002. **83**(12): p. 1697-702.
26. Mackay-Lyons, M.J. and L. Makrides, *Longitudinal changes in exercise capacity after stroke.* Arch Phys Med Rehabil, 2004. **85**(10): p. 1608-12.
27. Macko, R.F., et al., *Treadmill training improves fitness reserve in chronic stroke patients.* Arch Phys Med Rehabil, 2001. **82**(7): p. 879-84.
28. Saunders, D.H., C.A. Greig, and G.E. Mead, *Physical activity and exercise after stroke: review of multiple meaningful benefits.* Stroke, 2014. **45**(12): p. 3742-7.
29. Gjellesvik, T.I., et al., *Effects of High-Intensity Interval Training After Stroke (the HIIT-Stroke Study): A Multicenter Randomized Controlled Trial.* Arch Phys Med Rehabil, 2020. **101**(6): p. 939-947.
30. Marzolini, S., et al., *Effect of High-Intensity Interval Training and Moderate-Intensity Continuous Training in People With Poststroke Gait Dysfunction: A Randomized Clinical Trial.* J Am Heart Assoc, 2023: p. e031532.
31. Boyne, P., et al., *Effects of Exercise Intensity on Acute Circulating Molecular Responses Poststroke.* Neurorehabil Neural Repair, 2020. **34**(3): p. 222-234.
32. Boyne, P., et al., *Exercise intensity affects acute neurotrophic and neurophysiological responses poststroke.* J Appl Physiol (1985), 2019. **126**(2): p. 431-443.
33. Morton, A., et al., *Optimizing Recruitment Strategies and Physician Engagement for Stroke Recovery Research.* J Neurol Phys Ther, 2021. **45**(1): p. 41-45.
34. Boyne, P., Dunning, K., Carl, D., Gerson, M., Khoury, J., Rockwell, B., Keeton, G., Westover, J., Williams, A., McCarthy, M., Kissela, B., *High-Intensity Interval Training and Moderate-Intensity Continuous Training in Ambulatory Chronic Stroke: Feasibility Study.* Phys Ther, 2016. **96**(10): p. 1533-1544.
35. Buckley, B.J.R., et al., *Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Stroke.* Stroke, 2022. **53**(5): p. 1759-1763.
36. Billinger, S.A., B.Y. Tseng, and P.M. Kluding, *Modified total-body recumbent stepper exercise test for assessing peak oxygen consumption in people with chronic stroke.* Phys Ther, 2008. **88**(10): p. 1188-95.
37. Bayles, M.P., et al., *ACSM's exercise testing and prescription*. 2024, Wolters Kluwer,: Philadelphia, PA. p. 1 online resource.
38. Billinger, S.A., et al., *Recumbent stepper submaximal exercise test to predict peak oxygen uptake.* Med Sci Sports Exerc, 2012. **44**(8): p. 1539-1544.
39. Mattlage, A., Ashenden, A. L., Lentz, A. A., Rippee, M. A., Billinger, S. A., *Submaximal and Peak Cardiorespiratory Response After Moderate-High Intensity Exercise Training in Subacute Stroke.* Cardiopulmon Phys Ther J, 2013. **24**(3): p. 14-20.