CASE (Combating Alzheimer's through Sleep and Exercise) 202203931

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1) Objectives

The main objectives of this exploratory, hypothesis-generating trial are to:

1) assess whether improvements in sleep architecture (e.g., slow-wave sleep (SWS), rapid eye movement (REM) sleep), total sleep time, and quality (e.g., increased sleep efficiency, decreased sleep onset latency and restlessness [restless bouts/hour]) are associated with improved cognitive performance and improved biomarker panels for brain and cardiometabolic health;
2) evaluate the effects of structured, moderate-level aerobic and anaerobic exercise on cognitive performance and improved biomarker panels for brain and cardiometabolic health;
3) examine the combined, potentially synergistic effects of the sleep and exercise interventions on cognitive performance and biomarker panels for brain and cardiometabolic health; and
4) investigate the role of light exposure as a potential modulator of sleep parameters.

The central hypotheses of this trial are that:

1) lower baseline sleep architecture duration and quality measures as well as physical activity levels will be linked with poorer cognition and more adverse brain and cardiometabolic biomarker profiles at baseline;
2) improvements in sleep metrics (i.e., increased sleep efficiency, SWS, REM, and total sleep durations, as well as reduced onset latency and restlessness) will correspond to cognitive improvements and favorable biomarker changes during the eight-week intervention;
3) increased exercise will independently predict better cognitive, brain, and cardiometabolic health;
4) the combined sleep and exercise group will demonstrate greater improvements in cognitive function and biomarker profiles for brain and cardiometabolic health; and
5) these changes will be more pronounced in individuals with Mild Cognitive Impairment (MCI) compared to age- and sex-matched, cognitively normal (CN) controls.

Given the short duration, this trial is explicitly intended for signal detection, building on similar eight-week studies of behavioral interventions that have successfully detected early cognitive and physiological response patterns.

2) **Background**

Dementia is an increasingly critical public health risk, with over 55 million Americans at risk for the disease [1]. To stem the burden of Alzheimer's disease and related dementias (ADRDs), prophylactic and protective strategies such as physical activity and sleep interventions have been recommended to reduce the risk of cognitive decline and ADRD [2]. Previous research indicates that exercise improves cognition and lowers dementia risk [3, 4] and may be a promising intervention to address dementia risk in the general population. Moreover, sleep may reduce dementia risk. Specifically, previous work shows that greater levels of slow-wave sleep (SWS) were related to higher cognition [5]. However, little is known about the independent and combined effects exercise and sleep have on cognition and plasma brain (i.e., amyloid beta peptides 1-42 (Aß42), amyloid beta peptides 1-40 (Aß40), Aß42:Aß40 ratio, phosphorylated tau at threonine 217 (p-tau217), neurofilament light chain (NfL)) and cardiometabolic health (e.g., high-sensitivity C-reactive protein (hs-CRP), fasting total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, C-peptide, insulin, and glycated hemoglobin (HbA1c)). The proposed trial, therefore, aims to examine the independent and combined effects of exercise and sleep on cognition and markers of brain and cardiometabolic health.

Exercise and sleep are pathways that may ameliorate or even prevent cognitive decline and reduce AD risk. To our knowledge, few studies have investigated combined and longitudinal effects of sleep and exercise on AD risk over time to date. Therefore, this trial will significantly add to the scientific literature and may provide novel insights on minimizing AD risk through non-pharmaceutical, modifiable health behaviors. Findings may furthermore encourage additional, fully powered trials that can support findings of an actionable clinical intervention(s) to improve brain, cognitive, cardiometabolic, and sleep health, thereby mitigating AD risk in middle-aged older adults. In addition, with relevance to clinical care, the evaluation of difficulties in such tasks is crucially important to maintain independence in daily living.

Prior literature has shown that disruptions in higher-order cognitive functions, particularly memory consolidation followed by executive dysfunction, may predict an acceleration in cognitive decline and AD risk [6] and progression [7]. Simple, computer-based neuropsychological assessment could efficiently predict AD in the early stages. Compared to invasive and considerably pricier biomarkers such as Positron Emission Tomography (PET), computer-based diagnosis would provide

the greatest benefit in terms of cost and risk compared with other techniques. Additionally, computer diagnosis does not require discomfort from exposure to radiation, unlike PET scans, and would significantly increase accessibility, flexibility, and comfort of the method as an early screening tool. However, one limitation of augmented reality (AR)-based computer diagnosis is that many older people may be unfamiliar with user interfaces. This limitation, however, could be overcome by making the digital devices intuitive and user-friendly, limiting user interfaces, and emphasizing the AR, internet of things (IoT), and movement-based components of the AD diagnosis.

Our proposed study is innovative in *scope* (measuring the effect of a wearable sleep intervention and/or in-person exercise interventions on cognition and markers of brain and cardiometabolic health), *design* (in a randomized controlled trial design, combining novel, wearable intervention technology [Elemind Neuromodulation headband, which has been successful in improving slow-wave sleep, rapid eye movement sleep, and total sleep through intervention [8, 9]] and a moderate-intensity exercise intervention) and *methodology* (a suite of IoT devices).

3) **Inclusion and Exclusion Criteria**

Inclusion Criteria

To participate in this study, an individual must meet all the following criteria:

1. Aged 55-80 years at the time of the screening visit
2. Able to ambulate safely and independently
3. Able to safely perform moderate-intensity exercise as per the Physical Activity Readiness Questionnaire (PAR-Q, a validated exercise readiness questionnaire [10])
4. Able to wear and use Fitbit wristwatch and/or the Elemind Neuromodulation headband and Lys devices
5. Able to operate a digital device like mobile phone or computer
6. Able and willing to provide venous blood samples
7. Able to understand and speak English (our AR-based MCI diagnosis tool does not yet have capacity for other languages)
8. Able to self-report a history of cognitive changes or impairment
9. Be cognitively able (including those with and without MCI) and willing to provide informed consent
10. Body weight <400 pounds (<181.4kg) in order to safely operate the NuStep T4r Recumbent Stepper stationary bicycle [11]

Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Severe mobility limitations that prevent safe participation in moderate exercise protocols
2. Unstable or uncontrolled medical conditions (e.g., recent cardiovascular event (<6 months), cerebrovascular accident or transient ischemic attack (<6 months), active cancer, or uncontrolled diabetes) that pose safety concerns
3. Inability to complete intake screening procedures
4. Severe uncorrected hearing impairment—particularly if it precludes effective utilization of the Elemind Neuromodulation headband—and/or vision impairment that interferes with digital device usage or in-person exercise guidance
5. Determined to have Alzheimer's/dementia based on performance on the Quick Mild Cognitive Impairment (QMCI [12]; (see **Table 1**)).
6. Inability or unwillingness to learn or engage with digital devices (e.g., smartphone, Fitbit, Elemind, or Lys), even with staff support
7. Regular pre-study engagement in ≥150 minutes of moderate-level and/or ≥75 minutes of vigorous-level exercise per week based on Fitbit data obtained during the initial seven-day onboarding screening period
8. Determined to have sufficient sleep, as defined by a sleep efficiency mean of ≥80% [13]) based on Elemind Neuromodulation headband data obtained during the initial seven-day onboarding screening period
9. Current usage of disease-modifying therapy targeting amyloid (e.g., anti-amyloid monoclonal antibodies) or tau
10. Body weight ≥400 pounds (≥181.4kg), which would pose a safety risk during the operation of the NuStep recumbent stationary bicycle [11]

Table 1. QMCI Score Thresholds by Cognitive Status

	Aged ≤75, Education <12 years	**Aged ≤75, Education ≥12 years**	**Aged >75, Education <12 years**	**Aged >75, Education ≥12 years**
CN	≥66	≥70	≥64	≥64
MCI	55–65	58–69	51–63	52–63
Dementia	<55	<58	<50	<51

CN = cognitively normal; MCI = mild cognitive impairment; QMCI = Quick Mild Cognitive Impairment screen.

4) **Procedures Involved**

Combating Alzheimer's through Sleep and Exercise (CASE) is a single-center, three-arm, randomized trial that will investigate the effects of sleep, exercise, and a combination of these on cognitive function as well as brain and cardiometabolic biomarker outcomes in older adults with and without MCI. Participants will be randomly assigned via REDCap to one of three groups: (1) sleep-only, (2) exercise-only, or (3) combined sleep and exercise. Each group will receive intervention-specific digital tools: (1) all groups will receive a Fitbit to track physical activity, including the tracking of the in-person, biweekly, 60-minute exercise interventions; (2) the sleep-only and sleep+exercise groups will receive the Elemind Neuromodulation headband for personalized acoustic stimulation; and (3) the sleep-only and sleep+exercise groups will receive a Lys device for monitoring light exposure.

The intervention will span eight weeks and will follow structured phases, including: screening, baseline assessment, intervention, and follow-up. Full Digital Neuro-Signature Platform AR cognitive assessments will be used to assess cognition at baseline and Week 8 (post-intervention). Blood-based biomarkers will be collected via venipuncture at Quest Diagnostics at baseline and post-intervention (within 15–30 minutes of the final exercise session for participants assigned to interventions that involve exercise). Data from digital devices will be temporally synchronized using structured protocols to support integrated analysis, and raw sleep data will be reviewed for artifacts. Patient-Reported Outcomes Measurement Information System (PROMIS) surveys [14] and validated physical activity questionnaires (including the Physical Activity Scale for the Elderly (PASE [15]) and the Community Healthy Activities Model Program for Seniors (CHAMPS [16]) questionnaires) will be administered via REDCap at baseline (Week 0) and at week 8 during the in-person visits. The CASE study is designed to assess adherence, detect early efficacy signals, and explore behavioral mechanisms that may prevent or delay AD through modifiable behavioral interventions.

All participants will receive $50 at baseline (Week 0) and $50 at the conclusion (Week 8) visit, totaling up to $100 for full participation in the trial. Participants will be issued a reloadable debit card (ClinCard) that can be used for study-based compensation at the University of Miami. Funds will be loaded on the card according to the payment schedule. The study staff will provide specific information about how the card works. The company administering the card will

require a full name, address, and date of birth to be entered online for payment. This information will only be used for payment and communication purposes and will not be given to another company or linked to any of the study data. All prospective participants who pass pre-screening eligibility but are found to be ineligible after the initial 7-day onboarding screening period and are also not eligible for or interested in being reassigned to an alternative intervention group will receive $20 compensation for their efforts. Furthermore, participants will be reimbursed for either parking or via Metro passes at the conclusion of each in-person visit when applicable.

Screening & Consent

A trained research assistant will conduct a brief phone pre-screening with all prospective participants. During this call, the research assistant will collect key demographic information (e.g., age, sex, education level, and smartphone ownership) and administer two validated screening tools: the Quick Mild Cognitive Impairment screen (QMCI, a clinician-administered tool used to assess objective cognitive status [12]) and the Physical Activity Readiness Questionnaire (PAR-Q, which evaluates the participant's ability to safely engage in moderate exercise [10]; see **Table 2**). Both assessments will require fewer than five minutes to complete each. Participants must achieve a QMCI score at or above the specified age- and education-adjusted scoring thresholds that indicate either CN or MCI status (see **Table 1** [17, 18]) and report no contraindications to performing moderate-intensity exercise on the PAR-Q. Subjects who score below these thresholds will be excluded from the trial; no borderline adjudication process will be applied to ensure clarity and reproducibility.

Individuals meeting these pre-screening criteria will then be scheduled for an in-person or via a secure video conference screening visit to complete informed consent and further assess eligibility criteria via a seven-day screening period. Each prospective subject will be provided with a paper-based or digital copy of the signed informed consent document. Thereafter, prospective participants will be randomized into one of three arms and will receive (in-person or shipped via mail) intervention-specific wearable devices and will be instructed on how to use these devices. All prospective participants will receive Fitbit devices, while those assigned to the sleep or sleep+exercise interventions will receive an Elemind Neuromodulation headband to be used without stimulation during the initial 7-day screening period and a Lys device. Prospective participants in all groups will be asked to wear the Fitbit device continuously to establish baseline physical activity levels and to confirm sedentary to lightly active physical activity levels in order to satisfy eligibility criteria for those assigned to interventions that involve exercise;

those assigned to the sleep-only or sleep+exercise interventions will be asked to wear the Elemind Neuromodulation headband without stimulation while the device actively collects sleep data for seven consecutive nights to establish baseline sleep patterns, ensure comprehension of and comfortability with wearing the headband, and to confirm subquality sleep pre-intervention to satisfy eligibility criteria.

Prospective participants who are assigned to the sleep or sleep+exercise interventions and are determined to have good quality sleep after the onboarding period, as defined by the eligibility criteria, will either be reassigned to the exercise-only intervention (if found to engage in <150 minutes of moderate-level or <75 minutes of vigorous-level activity weekly via the Fitbit) or will be excluded from further participation and given $20 compensation. Prospective participants who are assigned to the exercise or sleep+exercise interventions and who are found to be active or very active, as defined by the eligibility criteria, will either be reassigned to the sleep-only intervention and be invited to undergo an additional seven-day onboarding screening duration with the Elemind Neuromodulation headband to determine sleep-specific eligibility or will be excluded from further participation and given $20 compensation. Prospective subjects who agree to undergo an additional seven-day screening period and are deemed to have good quality sleep pre-intervention will also be excluded from participation and given $20 compensation. All procedures will comply with the University of Miami Institutional Review Board (IRB) requirements and federal privacy protections. Subsequent to completing the onboarding screening period, eligible participants will be invited to complete an in-person baseline visit.

Table 2. Pre-screening Questionnaires

Basic Info Screening Form (eligibility Criteria)	Age, whether prospective subjects own and can operate a smartphone/computer device
Physical Activity Readiness Questionnaire (PAR-Q)	Safe for participants to perform moderate-level exercise. This will be the main factor in determining if it is safe to perform the moderate-intensity exercise routine for participants; an emergency plan is detailed later in the study
Quick Mild Cognitive Impairment screen (QMCI) 6-item	A clinician-administered tool used to assess objective cognitive status

Randomization

The design will follow CONSORT randomization guidelines [19]. Participants will be eligible for randomization once all baseline questionnaires are completed. Blocked randomization will be conducted using a randomization table. Subjects in each block will be assigned to one of three intervention arms, ensuring equal allocation between CN and MCI subjects in each group.

Data and Safety Monitoring Plan

Clinical site monitoring is a vital process that ensures the safety and well-being of human subjects participating in a clinical trial. Clinical site monitoring will be conducted to ensure that the reported trial data is accurate, complete, and verifiable. Site monitoring will also ensure that the trial is in full compliance with the approved protocol/amendment(s), Good Clinical Practices, and applicable regulatory requirements. During the study, a medical doctor will monitor participants who report experiencing medical issues. Should any medical issues arise, participants will be encouraged to seek treatment from the subject's primary healthcare provider(s) during study enrollment. There are no special considerations for biological data collected by the Quest system, as no biological material will be stored, collected, or analyzed at the University of Miami laboratory. Safety monitoring will include carefully assessing and reporting adverse events to the appropriate IRBs and Privacy Boards. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Baseline and Follow-up Visits

Prospective participants who provided written consent and are found to be eligible for participation at the conclusion of the 7-day onboarding screening period will undergo the following procedures in accordance with the intervention to which each subject was assigned:

Group 1 (Exercise Only)

- Participants randomized to the exercise-only group will engage in an eight-week, home- and site-based exercise intervention designed for older adults across a range of cognitive and physical function levels. The program was developed by a member of the research team (Dr. Kirk-Sanchez), who has more than 30 years of experience in geriatric rehabilitation. All site-based sessions will occur in person at the study facility under supervision of trained staff. Each week, participants will attend two 60-minute structured exercise sessions, consisting of aerobic training and resistance training. On

the remaining five days when subjects will not engage in structured exercise, subjects will be asked to engage in 30 minutes of moderate-intensity walking activities. In-lab exercise protocols will be fully standardized to ensure consistency of exercise dosage and fidelity across participants. The target exercise load will be 270 minutes of moderate intensity exercise weekly for 8 weeks. Although considered short-term exercise, this exercise dose has been shown to improve cerebral blood flow, regional brain volume, and brain-protective trophic factors [20].

- **Site-based protocol**. Participants will begin with a seven-day onboarding period, during which participants will wear the Fitbit continuously to establish baseline physical activity levels and to ensure initial eligibility criteria are satisfied. Subsequent to this initial observation and screening phase, subjects will participate in biweekly, in-person exercise sessions, which will be comprised of 60 minutes of stretching, aerobic, and resistance training exercises that will be supervised at all times by a trained research assistant. Specifically, exercise sessions will consist of a 10-minute warm-up, followed by 20 minutes of moderate-intensity aerobic exercise at 60–75% of estimated maximum heart rate (MHR). MHR will be estimated using Tanaka's formula (maxHR=208-(0.7*age)) [21] and the target heart rate (THR) will be calculated using Karvonen's formula to account for resting heart rate (RHR), where THR=((MHR-RHR)*% intensity)+RHR) [21]. Exercise will be performed on the NuStep recumbent bicycle. This is considered one of the safest modes of exercise for older adults as it allows total body engagement with low impact movement. In addition, the bike allows a secure seated position on a wide comfortable seat with back support, has a swivel seat to facilitate easy access, and has a the Stridelock system, which allows for additional security during entry and exit. Moderate-intensity aerobic training will be followed by 20 minutes of resistance training of major muscle groups with an emphasis on lower extremity resistance training one day each week and upper extremity resistance training at the second in-person session weekly. Exercise load will be at 60–80% of an estimated one repetition max using American College of Sports Medicine Guidelines [22]. Muscle groups that will be trained include biceps, triceps, deltoid, and latissimus dorsi for the upper extremity, and quadriceps, hamstrings, and gastrocnemius/soleus for the lower extremity. Resistance training exercises targeting the trunk will also be incorporated. Exercises will be conducted in supported standing, lying, or sitting positions, and the participants will be guarded by the research assistant at all times to ensure safety and decrease the risk of falling. Each exercise session will then conclude with 10 minutes of post-exercise stretching. Additional safety

measures include screening with the PAR-Q to ensure the participant is safe to exercise, and use of a finger Pulse oximeter to continuously monitor HR and O2 saturation.

- **Home-based protocol**. In addition to the twice weekly site-based exercise sessions, participants will be asked to include 30 minutes of walking at a moderate intensity on the remaining five days each week when participants do not complete the biweekly, in-person exercise sessions. This activity does not expose the participants to any additional risk, as independent community ambulation is an inclusion criterion.
- **Assessment of aerobic capacity**. Aerobic capacity will be measured at baseline and after 8 weeks of exercise using the six-minute walk test (6MWT). The 6MWT accurately estimates maximal oxygen uptake capacity (VO2max), using regression equations including distance walked, sex, age, and body mass index [23].
- **Cognitive Assessments**. Participants will complete the full-length, digital cognitive assessments at Week 0 (baseline) and Week 8 in a quiet testing room before commencing with their exercise session. These assessments will simulate real-world cognitive tasks and will yield high-resolution, domain-specific cognitive profiles.
- **Continuous Physical Activity Monitoring**. Participants will wear a Fitbit continuously throughout the study, including wake and sleep hours. Fitbit-derived data will be categorized into three activity domains:
    1) **Protocol-Guided Exercise (PGE):** Exercise occurring during supervised, in-lab sessions.
    2) **Non-Protocol Physical Activity (NPA):** Incidental movement and unsupervised activity outside scheduled sessions.
    3) **Total Physical Activity:** Combined PGE + NPA, derived from 24-hour Fitbit data.
- The primary Fitbit metric will be daily step count, a validated proxy for global movement shown to correlate with cognitive, brain, and cardiometabolic health outcomes in older adults [24]. A secondary metric, calories burned, will offer insight into the metabolic intensity of movement. Step count and caloric expenditure will be examined in relation to cognitive as well as brain and cardiometabolic biomarker outcomes. Analytical models will include PGE and NPA as independent predictors, which will be modeled separately and jointly to assess differential and additive contributions to primary (cognitive, brain, and cardiometabolic markers), secondary (sleep metrics and exercise measures), and tertiary (light exposure and psychosocial measures) outcomes.

- **Self-Reported Physical Activity**. To complement wearable-derived data and assess convergent validity between objective and subjective measures of physical activity, participants will complete two validated, self-reported instruments. The Physical Activity Scale for the Elderly (PASE; [15]) will be administered at Week 0 (baseline) and Week 8 (post-intervention). This questionnaire will capture the frequency, duration, and intensity of physical activity over the prior seven days. In addition, participants will complete the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire, which evaluates the effectiveness of an exercise intervention in community-dwelling older adults. From the CHAMPS questionnaire, a Metabolic Equivalent of Task (CHAMPS–MET) metric will be derived; this metric will be utilized to estimate weekly caloric expenditure [16]. The CHAMPS survey will also be administered at Week 0 (baseline) and Week 8 (post-intervention). The integration of these two tools will enable a comprehensive triangulation strategy to optimally evaluate alignment and potential discrepancies between perceived and actual physical activity. Discrepancy scores between self-reported and Fitbit data will be computed and examined as potential moderators or mediators of outcomes, particularly in relation to cognitive status or adherence.
- **Anthropometric Measurements Obtainment**. Height and weight measurements will be obtained on-site. Height will be measured twice at the baseline visit only, and an average of these two measurements will be considered each participant's final height measurement. In addition, weight will be measured by a Renpho digital scale at weeks 0 (baseline) and 8 (post-intervention follow-up visit). Similarly to height, weight will be measured twice at each visit, and an average of these two measurements will be considered each participant's final weight at the time of the visit. In any case where either the height or weight measurement(s) differ significantly between the first two measures (defined as >1.0 centimeters difference for height and >0.5 kilograms difference for weight between the initial two obtained readings), a third measurement will be obtained and incorporated into the average of the other 2 readings to determine the final height and weight from the participant at the time of the visit. From this, body mass index will subsequently be calculated as: weight (kilograms) / (height (meters))^2 and factored into the final analysis as a covariate.
- **Biomarker Collection Strategy**. Brain and cardiometabolic health will be assessed using a hybrid biospecimen collection protocol. Two venipuncture-based blood draws will be conducted through Quest Diagnostics, occurring at week 0 (pre-intervention) and week 8 (post-intervention) under standardized fasting conditions. To maximize participant safety and

minimize all possible influences of acute exercise [25], pre-intervention blood draws will be obtained no later than 7 days prior to, but no sooner than 24 hours before, the initiation of the first exercise session, and post-intervention blood draws will be obtained within 24–48 hours after completion of the final exercise session. No blood draws will occur on the same day as in-lab exercise. For all participants, plasma samples will be assessed for cardiometabolic risk, which will include high-sensitivity C-reactive protein (hs-CRP), glycated hemoglobin (HbA1c), and fasting total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, insulin, and C-peptide levels, which will provide time-sensitive insight into the inflammatory, glycemic, lipid, and insulin resistance markers across the intervention period. Furthermore, the extent of AD-associated neuropathology will be assessed at baseline via plasma samples, which will include amyloid beta peptide 1–42 (Aß1–42), Aß1–40, Aß1–42/Aß1–40 ratio, and phosphorylated tau at threonine 217 (p-tau217). These biomarkers will be subsequently integrated into a single analytical interpretation of AD risk, which has an 88% positive and 91% negative concordance with amyloid-PET-based results [26]. The aforementioned biomarkers will serve as staging and stratification variables, enabling the utilization of such biomarkers as covariates or effect moderators (e.g., assessing whether intervention response differs by baseline pathology status) without presuming measurable longitudinal change over the short intervention window. Additionally, to capture biologically meaningful change over an 8-week duration, plasma neurofilament light chain (NfL) will be obtained and measured at baseline and at post-intervention. Unlike the amyloid- or tau-based biomarkers, NfL reflects ongoing neuroaxonal stress and overall neurodegeneration and has demonstrated sensitivity to behavioral and lifestyle interventions, including exercise- and sleep-related alterations, over relatively short time periods (e.g., 8 weeks) [27]. Consequently, NfL is more appropriate for detecting intervention-related biological signals within the timeframe of this pilot study.

- **Temporal Synchronization and Data Integration**. Physical activity, cognitive function, and biomarker data will be aligned using a centralized time-stamped database. Sampling windows will be synchronized with protocol events (e.g., in-lab sessions, assessment points) to ensure precise temporal integration of physiological, cognitive, and behavioral data streams.
- **Data Safety Management**. All data will be stored in HIPAA-compliant systems. Fitbit and the Digital Neuro-Signature Platform data will be de-identified and linked using secure participant codes. Statistical models will

include age, sex, education, baseline sleep metrics, baseline physical activity levels, body mass index, and cognitive status as covariates.
- By integrating standardized, in-lab exercises, wearable technology, digital cognitive assessments, and multimodal biomarker data, this arm of the *CASE* study aims to explore the cognitive, brain, and cardiometabolic impacts induced by structured exercise in aging adults who are at higher risk for AD using a real-world, ecologically-valid framework.

Group 2 (Sleep Only)

- Participants randomized to the sleep-only group will participate in an eight-week intervention utilizing the Elemind Neuromodulation headband, an electroencephalography-based, non-invasive, wearable device designed to reduce onset latency through personalized acoustic stimulation that is tailored to the unique brainwaves of each individual. This arm is intended to assess the efficacy of a home-based neuromodulation strategy in older adults with varying cognitive and functional baselines.
- **Device Use and Sleep Monitoring**. Subjects will start with a seven-day onboarding screening period, during which participants will wear the Elemind Neuromodulation headband nightly without stimulation to passively establish a baseline sleep pattern and to ensure initial eligibility criteria is satisfied. Following this, the neuromodulation feature will be activated, and participants will be instructed to wear the device at least 3–4 nights per week for eight weeks. Each use will deliver bone conduction-based acoustic stimulation tailored to the participant's real-time brainwave activity. The headband will collect continuous data on multiple sleep metrics, including total sleep duration, sleep efficiency, sleep onset latency, restlessness, and time spent in various sleep stages (light (N1/N2), N3, REM) as well as total sleep duration. Sleep data will be delivered via the Elemind smartphone application. Raw data will be reviewed regularly for artifacts such as signal dropout and excessive motion. Nights with incomplete data (e.g., <4 hours of recording or ≥10% missing epochs) will be flagged and excluded from analysis and will prompt follow-up instructions or re-onboarding support. The Elemind Neuromodulation device's sleep staging outputs, while designed to approximate polysomnographic benchmarks, are considered proxies and will be interpreted accordingly.
- **Device Use and Physical Activity and Light Monitoring**. In addition, participants will wear the Lys device continuously throughout the eight-week trial period. The Lys device will measure the intensity, color, and

duration of light exposure to gain insights into the relationship between light, sleep, circadian cycles, and energy levels. This device works by communicating with the company's proprietary app, named Insight, to display light exposure data to the user as well as to provide the individual with goals and insights related to light and health. Additionally, Lys communicates with a separate app, called Collect, which will be used by the researchers to download data at the conclusion of the study. In addition, subjects in this group will also receive Fitbit devices and will be asked to wear the device continuously to passively gauge physical activity levels throughout the trial duration.

- **Cognitive Assessments**. Full-length, digital cognitive assessments (approximately 20 minutes) will be conducted at Week 0 and Week 8 in a quiet testing room at the University of Miami or, if unable/not preferred to complete in person, via a secure video conference with a trained research assistant.
- **Anthropometric Measurements Obtainment**. Height and weight measurements will be obtained on-site. Height will be measured twice at the baseline visit only, and an average of these two measurements will be considered each participant's final height measurement. In addition, weight will be measured by a Renpho digital scale at weeks 0 (baseline) and 8 (post-intervention follow-up visit). Similarly to height, weight will be measured twice at each visit, and an average of these two measurements will be considered each participant's final weight at the time of the visit. In any case where either the height or weight measurement(s) differ significantly between the first two measures (defined as >1.0 centimeters difference for height and >0.5 kilograms difference for weight between the initial two obtained readings), a third measurement will be obtained and incorporated into the average of the other 2 readings to determine the final height and weight from the participant at the time of the visit. From this, body mass index will subsequently be calculated as: weight (kilograms) / (height (meters))^2 and factored into the final analysis as a covariate.
- **Biomarker Collection Strategy**. Similar to the first arm, cardiometabolic and brain health will also be assessed using a hybrid biospecimen collection protocol in this arm. Specifically, two venipuncture-based blood draws will be conducted through Quest Diagnostics, occurring during week 0 (pre-intervention) and week 8 (post-intervention) after the final utilization of the Elemind Neuromodulation headband has been completed. Samples will be assessed for hs-CRP and HbA1c levels as well as fasting total cholesterol, HDL, LDL, triglycerides, insulin, and C-peptide levels, which will provide time-sensitive insight into the inflammatory, glycemic, lipid, and insulin

resistance markers across the intervention period. Changes in neuroaxonal stress and overall neurodegeneration from baseline will be assessed via plasma NfL levels at weeks 0 and 8. Furthermore, AD-linked neuropathology will be assessed at baseline only via plasma samples, including Aß1–42, Aß1–40, Aß1–42/Aß1–40 ratio, and p-tau217.

- **Missing Data and Adherence**. Participants missing ≥10% of required sleep intervention nights (defined as <22 nights of wearing the sleep intervention over the 8-week intervention period) will be flagged for sensitivity analyses. If a participant misses >2 consecutive weeks of data and/or fails to complete either of the full-length, digital cognitive assessments, participants will be excluded from per-protocol analyses but retained in intention-to-treat models. Multiple imputation will not be applied due to the small sample size; instead, pattern mixture modeling or last observation carried forward (LOCF) methods will be used where applicable.
- **Adherence and Continued Engagement**. Weekly (i.e. every ~7 days), phone or video check-ins (10–15 minutes) will be made to monitor engagement, support adherence, and troubleshoot technical issues.
- **Limitations**. This study will not include a sham stimulation control for the sleep-only group. The decision to forgo a sham condition reflects the real-world, comparative effectiveness design of the CASE study and prioritizes ecological validity over internal blinding. Nonetheless, the absence of participant blinding may introduce potential placebo effects. To address this analytically, expectancy-related influences will be modeled using self-reported perceived benefit measures as an additional covariate in the regression models. Sensitivity analyses will explore whether high expectancy ratings moderate intervention effects. Between-arm comparisons will further contextualize the potential role of non-specific treatment effects in observed outcomes.
- **Temporal Synchronization**. All data sources—including Elemind (sleep), Lys (light exposure), Fitbit (physical activity/exercise), and digital cognitive assessments (cognitive function)—will be time-stamped and aligned using a centralized database. Sampling frames will be linked to specific intervention events and assessment windows to enable a temporally precise integration of cognitive and sleep data streams.
- By integrating wearable neurotechnology, digital cognitive assessments, and remote monitoring within a structured intervention framework, this arm of the CASE study aims to evaluate the adherence and early efficacy signals of at-home sleep neuromodulation in aging adults.

Group 3 (Sleep and Exercise)

- Participants randomized to the combined intervention group will engage in both structured exercise sessions and sleep neuromodulation over an eight-week study period. This arm is designed to explore the additive and potentially synergistic effects of engaging in both interventions concurrently while assessing adherence and participant burden, which will, in turn, inform future multimodal approaches to cognitive aging and AD prevention.
- **Protocol Structure and Considerations**. To reduce participant burden and improve standardization, in-lab exercise sessions and cognitive assessments will follow the same cadence and structure as in the exercise-only arm: completion of full cognitive assessments at baseline (week 0) and follow up (Week 8) followed by the first (baseline) and last (Week 8 post-intervention visit) completion of the exercise sessions. In between time, twice weekly, 60-minute, supervised sessions focusing on aerobic and resistance training as well as a home-based walking program will be completed. Participants will also wear the Elemind Neuromodulation headband for a total of at least 3–4 nights per week across the eight-week period, with an initial 7-day, passive, onboarding screening phase of wearing the headband nightly without stimulation in combination with wearing the Fitbit device continuously to establish baseline sleep patterns, physical activity levels, and ensure that eligibility criteria are satisfied. Finally, subjects will also wear the Fitbit and Lys devices continuously throughout the 8-week trial period.
- To manage cumulative burden, scheduling flexibility will be emphasized. Although participants will be offered a choice of days and times for in-lab sessions to fit each participant's weekly routines, morning times will be strongly encouraged across all participants, as prior work has suggested that older adults generally show better cognitive and exercise performance in the mornings [28, 29]; this will further improve standardization. Staff will work closely with participants to accommodate visit times, provide transportation assistance where applicable, and ensure ample time for recovery between activities.
- For improved standardization, participants in this group will also be asked to attend in-person exercise sessions on the days after they wore the Elemind Neuromodulation headband the preceding night.
- **Anthropometric Measurements Obtainment**. Just as in the other arms, height and weight measurements will be obtained on-site. Height will be measured twice at the baseline visit only, and an average of these two measurements will be considered each participant's final height measurement. In addition, weight will be measured by a Renpho digital scale at weeks 0 (baseline) and 8 (post-intervention follow-up visit). Similarly to

height, weight will be measured twice at each visit, and an average of these two measurements will be considered each participant's final weight at the time of the visit. In any case where either the height or weight measurement(s) differ significantly between the first two measures (defined as >1.0 centimeters difference for height and >0.5 kilograms difference for weight between the initial two obtained readings), a third measurement will be obtained and incorporated into the average of the other 2 readings to determine the final height and weight from the participant at the time of the visit. From this, body mass index will subsequently be calculated as: weight (kilograms) / (height (meters))^2 and factored into the final analysis as a covariate.

- **Biomarker Collection Strategy**. Biomarker collection through Quest Diagnostics (venipuncture at Week 0 and Week 8) will be conducted following the aforementioned procedures, with attention to minimizing scheduling conflicts with intervention activities.
- **Analysis Strategy**. This arm enables a unique opportunity to assess both the independent and combined contributions of sleep and exercise to cognitive, brain, and cardiometabolic outcomes. Statistical models will include main effects for sleep (e.g., adherence to Elemind usage), exercise (e.g., PGE, NPA), and interaction terms to evaluate additive or synergistic effects. Dose-response relationships will be explored using adherence metrics and physiological markers (e.g., heart rate during exercise, sleep efficiency). Adherence to both modalities will be summarized descriptively and modeled as predictors in multivariable analyses of primary outcomes.

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5) Measures/Instruments

Quest Diagnostics Blood Draw

Quest is a laboratory company that provides blood drawing and testing services. They provide a service in which participants can go to a location for blood sample collection. This de-identified data collected by Quest (biomarker data linked to a

participant by a study ID) is consented to be shared by the participant to the study team. These tests will measure:

- Total Cholesterol
- HDL
- LDL
- Triglycerides
- hs-CRP
- HbA1c
- C-peptide
- Insulin
- NfL
- Aß1-42 (baseline only)
- Aß1-40 (baseline only)
- Aß1-42:Aß1-40 ratio (baseline only)
- p-tau217 (baseline only)

All Quest Diagnostics' testing locations are appropriately licensed/certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88) and as required by certain State laboratory licensure programs. In addition, Quest Diagnostics' Regional and Esoteric Reference Laboratories are accredited by the College of American Pathologists (CAP).



Figure 1: The Fitbit fitness tracker, worn on the wrist.



Figure 2: Elemind Neuromodulation headband.



Figure 3: The Lys wearable device, clipped to clothing.



Figure 4: The Altoida cognitive testing platform, demonstrated on a smart device.

Fitbit Wearable Metrics

Consumer-grade Fitbit devices have demonstrated acceptable validity and reliability for measuring steps and energy expenditure in older adults. In controlled laboratory settings, Fitbit-measured steps agreed within ± 3% of observed counts; in free-living conditions, deviations remained within approximately ± 10% of research-grade accelerometers (e.g., actigraphy [30]). Prior evidence indicates that step counts correlate well with self-reported metrics—specifically, Fitbit steps with the PASE questionnaire and Fitbit calories burned with the CHAMPS–MET metric, particularly in older adult populations [24]. While Fitbit may underestimate steps at slower gait speeds [31], overall metrics are sufficiently reliable for longitudinal monitoring in aging cohorts. Data collection from this device will consist of two steps: (1) a period of data collection while participants initially wear Fitbit for seven consecutive days before the intervention is implemented and (2) subsequent data collection while participants continue wearing Fitbit throughout the intervening period. Similarly to the interventions that include exercise, participants in the sleep-only group will also be asked to continuously wear the device throughout the 8-week trial duration to ensure that physical activity levels do not confound the effects of sleep.

It should be noted that there is a considerable paucity of evidence in the prevailing body of literature assessing how well Fitbit-derived metrics correlate

with PASE and CHAMPS-MET scores in upper middle-aged adults (i.e., 55–64 years). As a result of this age-specific validation gap, the current trial will combine Fitbit metrics (e.g., step counts and caloric expenditure) with self-reported physical activity data from the PASE and CHAMPS questionnaires; this approach will enable a more comprehensive assessment of physical activity patterns and provide an opportunity to compare and interpret agreement between objective and self-reported measures within this cohort. The paucity of evidence that has assessed these correlations with the inclusion of middle-aged and older adult samples has generally found moderate relationships between Fitbit-derived step counts and PASE scores as well as between Fitbit-derived estimated energy expenditure and CHAMPS-derived MET values [24].

Elemind Neuromodulation Headband

The Elemind Neuromodulation headband is a wearable device that utilizes noninvasive, electroencephalography-based (EEG-based) technology to induce a sleep state more rapidly via personalized acoustic stimulation (see **Figure 2**). Specifically, the headband uses a closed-loop system, meaning that the headband conveys stimulation based upon recorded neural activity in order to modulate real-time oscillating circuits at the macroscopic level [32]. Technologies that utilize closed-loop systems have been shown to be a superior approach to open-loop systems for disease treatment in prior work [33]. This device uses five dry, flexible EEG electrodes — including three recording electrodes that are positioned at the Fpz and Fp1/2 electrodes sites in accordance with the 10–20 International System of electrode placement and two silicone rubber-based, linked reference electrodes located at the mastoids — to measure neural activity during sleep and provide an estimation of the phases of real-time neural oscillations [34, 35].

The headband generates a sound pulse by identifying alpha neural oscillations in real-time through endpoint-corrected Hilbert Transform algorithm, a signal processing advancement that is independent of oscillation sources and utilizes an infinite impulse response causal bandpass filter [32]. The headband furthermore utilizes a bone-conduction driver built into the center of the headband, which anatomically corresponds to the central forehead, to deliver auditory stimulation that is locked to phases of brainwave activity [34, 35]; this strategy has been found to impact continuous cortical oscillatory activity in prior studies [36, 37], including in older adults [36]. This method has, in turn, been shown to improve sleep for not only SWS oscillations [34, 36, 38] but also for oscillations across all sleep stages [35].

The Elemind Neuromodulation headband can be utilized in conjunction with machine learning approaches to optimize personalized treatments [32]. As such,

the user-programmed device will use Bluetooth low energy or a direct USB-C connection to control the device and transfer data obtained by the headband to the Elemind application on a smartphone [34, 35], which will collect sleep metrics, including: (1) total sleep duration, (2) sleep efficiency, (3) sleep architecture (i.e., durations and percentage of total sleep durations spent in each sleep stage, including the light non-rapid eye movement stages of sleep (i.e., N1/N2), SWS, and REM sleep architecture); (4) sleep onset latency; and (5) restlessness (number of restless bout(s) per hour). The headband device will be sent to participants at baseline and collected at the end of the study to analyze the sleep data. This intervention process will consist of two steps: (1) a period of data collection while participants initially wear the headband without stimulation for seven consecutive days and (2) subsequent data collection while participants continue wearing the Elemind Neuromodulation headband intervention for at least three to four days per week for eight weeks.

At the end of the analysis phase, the Elemind app will deliver a sleep report that includes a summary of each week's aforementioned sleep data. As each participant must have their own unique accounts to access the data associated with the utilization of the Elemind Neuromodulation device, there will be no data breach risk between participants who use the same Elemind device after a prior participant has completed their duration in the trial.

Lys

Lys is a coin-sized device which tracks lux and color levels through sensors aiming to replicate the eye's photoreceptors (see **Figure 3**). This device clips onto clothing or close-contact accessories (e.g., purse strap) and tracks light information throughout the day. The Lys devices measures the intensity, color, and duration of light exposure to gain insight about the relationship between light, sleep, circadian cycles, and energy levels. The Lys device communicates with the company's proprietary app, named Insight, to display light exposure data to the user, as well as provide the user with goals and insights related to light and health. The Lys device also communicates with a separate app, called Collect, which is used by the study team to download data at the conclusion of the study. The Lys device has been validated in previous literature and has been used in other studies of this nature (e.g., [39]).

Augmented Reality Cognitive Assessment Platform

The augmented reality platform delivers a Digital Neuro-Signature (DNS) based on >700 sensor-derived digital biomarkers captured through brief (10–20

minute), gamified cognitive tasks that simulate real-world activities [40] (see **Figure 4**). The DNS has demonstrated high sensitivity (≈0.91) and specificity (≈0.82) in detecting MCI and early AD progression as well as a predictive accuracy of approximately 94% for conversion risk to AD within aging cohorts in prior work. For instance, a longitudinal validation study (*N*=525) showed strong correlations with traditional neuropsychological tests, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), and showed that DNS outperformed conventional tools in detecting early cognitive change [41]. The Augmented Reality (AR)-based Cognitive Assessment Platform provides reliable, ecologically-valid cognitive phenotyping suitable for remote, high-frequency, digital health studies.

Digital Neuro-Signature

Altoida's Digital Neuro-Signature (DNS) cognitive assessments, which are suitable for both iPhone iOS and Android devices, are AR technologies that test a participant's cognitive and functional aptitude via a self-learning (machine learning) algorithm. Cognitive scores will be assessed during baseline and follow-up at the participants' homes using an application on a smart device. Participants will be asked to perform tasks using virtual reality representations on each subject's smartphone's camera. Using movement and response data plugged into machine learning systems, the service will provide a validated measure of MCI/AD risk, which will be shared with the study team and participants through a computer dashboard and through the app, respectively. The app will include (but not limited to) three major cognitive functions: (1) spatial memory, (2) prospective memory, and (3) executive function. All data will be automatically transmitted to the study team on an encrypted dashboard. The DNS cognitive assessments have been validated in previous literature (e.g., [42]).

Study Questionnaires

Questionnaires will be administered to gather demographic information, mental health status, health behavior information (sleep and physical activity/exercise) and cognitive status at baseline (Week 0) and at Week 8. Questionnaires will also be administered during screening to confirm eligibility for the study. These questionnaires will be used in conjuncture with our Elemind Neuromodulation headbands, Altoida, Fitbit, Lys, and biomarker readings to gather an accurate picture of sleep, physical activity/exercise, markers for brain and cardiometabolic health, and cognitive impairment risk. These questionnaires will be administered in person by a trained research assistant. All questionnaires have

been validated in previous literature. Subjects in all three groups will be administered questionnaires.

Physical Activity Scale for the Elderly (PASE) Questionnaire

The PASE Questionnaire will only be administered to participants assigned to interventions involving exercise. The PASE is a validated, self-report instrument that is widely used to assess physical activity. The PASE Questionnaire was originally designated for community-dwelling adults aged ≥ 65 years but has been subsequently validated in adults aged 45–64 years [43]; this questionnaire has demonstrated high test-retest reliability, with intraclass correlation coefficients (ICC) found to be $r = 0.75$ (95% CI = 0.69–0.80) over 3–7 weeks [15]. Short-interval reliability (10–14 days) has shown excellent reproducibility with ICCs, which range from 0.93–0.99 in prior work [44, 45]. Furthermore, construct validity is moderately supported: correlations with accelerometer-measured physical activity (steps, energy expenditure) range from $r \approx 0.30$–0.61 [46]. While internal consistency varies across activity domains ($\alpha \approx 0.69$–0.99 [15, 44]), the total score remains robust for classifying overall activity levels in older populations. Given the robustness of the PASE questionnaire across older adult populations, similar reliability is expected in upper middle-aged adults (55–64 years).

Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaire

Similarly to the PASE questionnaire, the CHAMPS questionnaire will also be administered only to participants assigned to interventions involving exercise. The CHAMPS questionnaire is a validated, self-reported instrument that was originally designed to evaluate the effectiveness of an exercise intervention in community-dwelling older adults aged ≥ 65 years but has subsequently been demonstrated to be a valid tool to utilize for middle-aged participants as well [47, 48]. From the CHAMPS questionnaire, a Metabolic Equivalent of Task (CHAMPS–MET) metric can be derived. The CHAMPS-MET metric will be utilized to estimate weekly caloric expenditure [16]. The CHAMPS questionnaire has demonstrated acceptable construct validity and reliability in older adult cohorts, with reported correlations of $r \approx 0.23$–0.55 when compared with accelerometer-based measures or functional health indicators [16, 47]. The CHAMPS questionnaire effectively captures activities typical of older adults' daily routines and complements objective, wearable metrics.

Table 3. Timeline of Questionnaires Provided and Bloodwork Schedule

Variable	Screening	Baseline	6-week
Basic Info Screening Form (eligibility criteria)	X		
Physical Activity Readiness Questionnaire (PAR-Q)	X		
Quick Mild Cognitive Impairment screen (QMCI), 6-item	X		
Demographic Questionnaire		X	
Medical History Questionnaire		X	
Cross Ethnic-Racial Identity Scale		X	
PROMIS Cognitive Function - Abilities Subset 4a short form		X	X
PROMIS Sleep Disturbance 4a short form		X	X
PROMIS Sleep-related Impairment 4a short form		X	X
PROMIS Emotional Support 4a short form		X	X
PROMIS Emotional Distress-Depression 4a short form		X	X
PROMIS Emotional Distress-Anxiety 4a short form		X	X
PROMIS Social Isolation 4a short form		X	X
PROMIS General Life Satisfaction 5a short form		X	X
PASE Physical Activity Questionnaire (issued to subjects assigned to interventions involving exercise only)		X	X
CHAMPS-MET Physical Activity Questionnaire (issued to subjects assigned to interventions involving exercise only)		X	X
Biomarker Data		X	X

Total Cholesterol		X	X
High Density Lipoproteins		X	X
Low Density Lipoproteins		X	X
Triglycerides		X	X
High-sensitivity C-reactive protein		X	X
Glycated Hemoglobin		X	X
C-peptide		X	X
Insulin		X	X
NfL		X	X
Amyloid Beta Peptide 1-42		X	
Amyloid Beta Peptide 1-40		X	
Amyloid Beta Peptide 1-42:Amyloid Beta Peptide 1-40 Ratio		X	
Phosphorylated Tau at Threonine 217		X	

PROMIS = Patient-Reported Outcomes Measurement Information System.

6) **Data and Specimen Banking**

☒ This section is not applicable. This research is not banking data or specimens for future use.

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. Study oversight will be under the overview of the PI.

For the brain and cardiometabolic biomarkers, there are no special considerations for specimen management; biological data collected by the Quest system is between that company and the participant through the mail (no biological material will be stored, collected, or analyzed at the University of Miami lab).

Clinical monitoring guidelines will be in place. Our study physician, Dr. Alberto Ramos, a medical doctor, will monitor participants who may experience medical problems while enrolled in the study. Participants will be encouraged to seek

treatment from their primary healthcare providers while in the study. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently-approved protocol/amendment(s), with Good Clinical Practices and applicable regulatory requirement(s).

7) Statistical Analysis Plan

Power and Sample Size Considerations

This trial is designed to be an exploratory, hypothesis-generating randomized controlled trial. Given the exploratory nature of this three-arm trial, a sample size of 60 participants (20 per group) was selected for this trial to balance feasibility with the ability to detect preliminary signals across intervention arms. Power analyses were conducted via simulation for linear mixed-effects models (LMMs) using estimated parameters relevant to repeated cognitive and biomarker outcomes measured at two time points (baseline (week 0) and 8 weeks). Assuming a moderate effect size (Cohen's $f^2 = 0.25$), $\alpha = 0.05$, a compound symmetry covariance structure, and no attrition, this sample size yields approximately 60–65% power to detect a significant group × time interaction. While this power is modest, it is sufficient to estimate effect sizes with reasonable precision and assess trends across intervention arms. Since LMMs maximize available data and accommodate unbalanced designs and missing data, LMMs will be preferred over repeated measures ANOVA for small-sample trials with incomplete follow-up. Results from this study will guide power calculations and design refinements for a fully powered randomized controlled trial. As generally recommended for early-phase behavioral intervention studies, this trial's emphasis will be placed on effect sizes and confidence intervals instead of solely statistical significance.

Analysis Plan

This study is designed as a three-arm, parallel-group trial comparing the effects of an 8-week exercise intervention (group 1), sleep intervention (group 2), and combined sleep + exercise intervention (group 3) on cognitive performance and biomarkers for brain and cardiometabolic health in older adults with MCI or no cognitive impairment. A total of 60 participants (20 per group) will be enrolled. All analyses will be conducted using IBM SPSS Statistics (Version 31.0.0.0; IBM Corp., Armonk, NY, USA). The primary analytic goal is to determine which intervention arm may demonstrate the greatest improvements in cognitive function

and biomarker profiles. Descriptive statistics (means, standard deviations, medians, interquartile ranges, and proportions) will be used to summarize demographic characteristics, intervention adherence, and baseline measures. Primary outcomes will include changes in cognitive domain-specific and global cognition scores from the digital cognitive assessments and changes in biomarkers for brain (NfL) and cardiometabolic health (HbA1c, hs-CRP, C-peptide, insulin, total cholesterol, HDL, LDL, triglycerides). Secondary outcomes will include changes in sleep metrics (e.g., sleep efficiency, SWS, REM sleep, and total sleep durations, onset latency, and restlessness, as measured via Elemind) and physical activity/exercise levels (PGE and NPA via Fitbit). Tertiary outcomes will include the role of light exposure (measured via Lys) as a potential modulator of sleep parameters and psychosocial measures (e.g., PROMIS Depression, Social Isolation).

Primary group comparisons will be conducted using LMMs, which offer flexibility for handling repeated measures, unbalanced data, and missingness under the Missing at Random assumption. Each LMM will include fixed effects for group (sleep, exercise, combined sleep + exercise), time (baseline, 8-week follow-up), and the interaction term between group × time. Subject-specific random intercepts will be included to account for intra-individual correlation over time. The main test of intervention efficacy will be the group × time interaction term. To evaluate whether improvements in biomarkers (e.g., HbA1c, hs-CRP) moderate the effects of the interventions on cognitive outcomes, exploratory moderation models will be conducted. These models will include biomarker change scores, group assignment, and group × biomarker interaction terms as predictors of cognitive change. Moderation models will use PROCESS v5.0 Macro for SPSS with bias-corrected bootstrapping (5,000 resamples). Significant interactions will be probed using Johnson-Neyman techniques.

Given the small sample size, power for detecting small effects will be limited. Thus, all models will report estimated effect sizes (Cohen's d, partial η^2), 95% confidence intervals, and significance levels (α=0.05). No corrections for multiple comparisons will be applied to primary outcomes; however, for secondary and exploratory outcomes, a Benjamini–Hochberg false discovery rate (FDR) correction will be used to control for Type I error. Composite indices may be created to reduce variable dimensionality. For cognitive outcomes, domain-specific cognitive function scores will be z-scored and aggregated into a global composite score. For blood-based biomarkers, z-scored values will be averaged to create an overall plasma-based AD risk index as well as a cardiometabolic risk index for all subjects.

Missing data will be handled using maximum likelihood estimation within LMMs. For summary scores or self-reported questionnaires with partially missing responses, scale-specific rules will be applied, if available. Participants missing

more than 2 weeks of intervention will be excluded from per-protocol models but retained in intention-to-treat analyses. Missingness patterns will be analyzed and classified as Missing Completely at Random (MCAR), Missing at Random (MAR), or Missing Not at Random (MNAR). All assumptions for normality, linearity, and homoscedasticity will be checked using residual plots and Kolmogorov–Smirnov tests. Skewed variables (e.g., hs-CRP) will be square root- or log-transformed prior to modeling. Outliers will be identified using leverage and Cook's distance, and sensitivity analyses will be performed with and without influential points.

As an alternative analytic strategy, if models fail to yield significant results due to insufficient power or high variability, effect sizes and confidence intervals (CIs) will be emphasized. A simplified analysis approach using ANCOVA (controlling for baseline scores) will be explored for key outcomes. Lastly, pattern mixture modeling may be used to examine intervention effects under different missing data assumptions.

8) **Risks to Subjects**

The general risks that are involved in this study are related to moderate-intensity exercise. Moderate-intensity exercise may cause muscle soreness, dizziness, or shortness of breath. In rare instances, exercise tests may cause chest pain, tightness, or a change in vital signs. There is mild risk to privacy regarding the demographic information of participants, but there are no variables that could be used to identify a participant. There may also be mild discomfort of wearing devices, but no more so than a normal headband or wristband. Participants may also feel mild discomfort when drawing the blood sample. Our study MD will review all test results. The participant will be asked to follow-up with their primary care physician in the event of a clinically significant result. This will be documented as an Adverse Event or Serious Adverse Event.

In the event of a clinically significant result, participants will be advised to contact the primary care physician.

Serious Adverse Events

For this study, a "Serious Adverse Event" is defined as any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or

disease temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Although the minimal risks inherent to this study are not expected to result in risk for Serious Adverse Events, in the unlikely instance of a Serious Adverse Event occurring, this event will be promptly reported to the IRB within seven days. Any other unanticipated problem not defined as a Serious Adverse Event will be reported to the IRB within fourteen days of occurrence.

Given the age of participants in the study population and the moderate intensity of the exercise intervention (at the same time giving consideration to the minimal risks of the nature of this exercise), Serious Adverse Events will be collected for this study beginning at the commencement of the intervention and 2 days after the conclusion of the intervention.

9) **Potential Benefits to Subjects**

Individuals participating in this study may benefit in terms of brain health, cardiovascular/aerobic health, sleep health, and cognitive scores.

10) **Vulnerable Populations**

There are no vulnerable populations in this study. Although we are studying Alzheimer's risk, participants are excluded if they meet the criteria for AD/dementia diagnosis.

11) **Setting**

All prospective participants who pass pre-screening eligibility criteria will be invited to be have the study explained to them and will be consented in person or via a secure video conference, randomized into one of three interventional groups, oriented to the devices that correspond to the intervention to which each subject was assigned, and engage in a 7-day onboarding screening period to further determine eligibility and establish baseline sleep and/or physical activity/exercise levels. If determined to satisfy all eligibility criteria, participants who are randomized into the exercise or sleep+exercise interventions will complete all questionnaires, blood draws, and intervention-specific procedures at baseline and at week 8 (post-intervention) in person in a lab space at the University of Miami. Furthermore, participants will conduct all exercise sessions biweekly for 8

weeks in a laboratory space at the University of Miami and will be continuously monitored during all exercise sessions and will also do all surveys in person. The participants in the sleep intervention will be invited and encouraged to return in-person to complete all questionnaires and blood draws in a lab space at the University of Miami at baseline and week 8 (post-intervention). If participants in this group have difficulty returning to the study site for baseline and/or the follow-up visit, participants in this intervention will be offered the alternative option of completing questionnaires virtually via a secure video conference with a trained research assistant for one or both visits, if absolutely necessary. All procedures in the sleep intervention will otherwise be conducted at home as instructed.

12) **Resources Available**

The small team running this study (consisting of Dr.'s Azizi Seixas, Debbie Chung, and Brittany Larsen) have years of experience running sleep studies as well as experience in the wearable devices field. They have published extensively on these topics and successfully completed studies with similar workflows. **Dr. Seixas has spent several years (10+) heading studies and collecting data with this population and has produced several NIH-funded studies.** This study will be using an MD associated with the University of Miami (Dr. Albert Ramos) to review and oversee clinical outcomes. Dr. Ramos will be acting as a consultant for this study. Dr. Neva Kirk-Sanchez will also be acting as a consultant for this study by advising the team about how to set up optimal short-term exercise interventions in older adults who are at higher risk for AD.

13) **Prior Approvals**

No prior approvals are necessary for this study.

14) **Recruitment Methods**

A total of 60 participants, comprised of approximately 30 CN older adults and 30 older adults with MCI, will be enrolled in this study. Recruitment strategies will consist of a combination of the following:

1) Participants will be recruited from existing studies and research registries maintained by the Translational Sleep and Circadian Sciences (TSCS) Laboratory at the University of Miami Miller School of Medicine. Specifically, a waiver of

documentation of consent has been requested for three studies in progress that have been established by this team—ESSENTIAL, DORMIR, and MOSAIC (IRB ID 20210485, 20211142, and 20210569, respectively). All individuals considered for enrollment will have previously consented to be contacted for future research opportunities. Initial contact will be made via phone by trained study personnel to confirm interest and screen for eligibility.

2) Recruitment will include referrals of prospective participants with a diagnosis of mild cognitive impairment (MCI) from the Division of Cognitive Neurology at the University of Miami, as well as from other treating physicians within the University of Miami Health System (UHealth) and affiliated clinical practices who care for patients with an MCI diagnosis. Referring clinicians will be provided with IRB-approved recruitment materials (i.e., study flyers and a brief study summary) to share with potentially eligible patients in the course of routine clinical care. Treating physicians are members of the patient's care team and may therefore introduce the study directly; however, no protected health information (PHI) will be disclosed to the study team by a referring provider unless (a) the patient has given the treating clinician verbal permission to release his or her name and contact information to the study team for research recruitment purposes, or (b) such disclosure is permitted under the partial waiver of HIPAA authorization requested herein. Interested patients may also self-refer by contacting study personnel directly using the information provided on the recruitment materials. All referred individuals will undergo the same telephone pre-screening procedures described above, and referral by a treating physician will confer no expectation or obligation of enrollment.

3) Moreover, flyers and social media advertisements will be distributed throughout southern Florida to further aid in recruitment efforts.

4) This trial will participate in the University of Miami's Consent to Contact (CTC) program, which allows approved researchers to access a database of UHealth patients who have agreed to be contacted about participating in clinical research studies. Consent to Contact is hereby listed as an approved recruitment method for this protocol. Following IRB approval of this modification, the study team will submit the required REDCap request to the CTC Operational Committee (CTCOC) for access. Prospective participants will be identified using study-specific criteria, including ICD-10 diagnosis codes corresponding to mild cognitive impairment, an age range of 55–80 years, and a defined service date range. A partial waiver of HIPAA authorization is requested to permit trained study personnel to access and review the limited PHI necessary to identify and contact potentially eligible patients. Initial contact will be made by telephone using the IRB-approved CTC phone script and accompanying sample dialogues. All study personnel who will contact prospective participants are identified in the Study Team section of this

protocol and have completed UHealth HIPAA Privacy and Security training. Participant lists obtained through the CTC program will be retained for the approved 90-day access period, enrollment outcomes will be tracked in REDCap as required by the CTCOC, and any subsequent request for extension, data refresh, or modification of search criteria will be submitted as a formal modification in IBISResearch where required.

Recruitment and enrollment procedures will comply with all institutional and federal guidelines, including the Health Insurance Portability and Accountability Act (HIPAA), to ensure privacy and confidentiality of all health information obtained. Eligible participants will be equally randomized (*n*=20 per group) into three study arms: sleep-only, exercise-only, or combined sleep and exercise. Stratified randomization by cognitive status will be employed to ensure balanced representation across groups (i.e., each group will be comprised of 10 CN participants and 10 participants with MCI).

15) **Confidentiality**

Choose the statements below that are applicable to this research:

15(a). ☐ Data will be collected from the EMR or subjects at UHealth or JHS.

☒ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB. (Complete Section 17 below)

15(b). Data collected:

☐ Will not include Protected Health information or Personally Identifiable Information

☒ Will include Protected Health information or Personally Identifiable Information

15(c). How will the research store the data?

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)
☒ On a cloud-based storage system that is approved by the University of Miami
☒ Other, specify: REDCAP data management system.

Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that **does not include any** indirect or direct identifiers (listed in the instructions for Section 15 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 15 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. **The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.**

Biospecimens

☐ Not applicable. No biospecimens will be collected

☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☐ *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.

☒ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to

the individual subject's identity maintain separately from the data and/or bio-specimen.

15d. Jackson Health System additional requirement

X This section is not applicable because the research is not collecting health information from JHS under a waiver of authorization (without obtaining a HIPAA authorization from the participant)

If health information, including Protected Health Information and/or Personally Identifiable Information are collected from JHS without a signed authorization from the subject (with a waiver of authorization from an IRB or Privacy Board), you must agree to the following:

☐ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research with a waiver of the requirement for an authorization under HIPAA shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 15 of this protocol.

If the data obtained for this research will be acquired from a retrospective "chart review" involving health information from JHS with a waiver of authorization (without obtaining a signed HIPAA authorization from the subject) then the data and the link and/or key to each subject's identity shall only be maintained in the secure JHS SharePoint environment made available by JHS.

16) **Provisions to Protect the Privacy Interests of Subjects**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

Information that will be relevant to HIPAA. All wearable devices are moved in a HIPAA-compliant network. Quest data exchange is HIPAA compliant.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Translational Sleep and Circadian Science lab at University of Miami Miller School of Medicine. This transmitted data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be used by clinical sites and by Translational Sleep and Circadian Science Lab and Media Innovation Lab at the University of Miami. Research staff will ensure that all information will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Translational Sleep and Circadian Science lab and Media Innovation Lab at University of Miami Jackson Health System.

- Intended Use: Samples and data collected under this protocol may be used to study sleep via an Elemind Neuromodulation device and exercise from Fitbit, light data from the Lys device, biomarkers for brain and cardiometabolic health, and cognition from Altoida's Digital Neuro-Signature assessments.

Device Tracking and Sensing: We will use Fitbit and the Elemind Neuromodulation headband, as well as the Lys device. De-identified participant data will be stored on the respective company highly-secured database, and participants will share their data with study team.

Data collected for this study will be analyzed and stored at the Quest Diagnostics laboratory, the Quanum portal, and within secure IT-approved systems. After the study is completed, the data will be destroyed. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Copies of the electronic Case Report Form (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents, or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

This study will comply with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. This policy requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

QC procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory

requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

17) **Waiver of Authorization for Use and Disclosure of Protected Health Information (HIPAA)**

☐ A waiver of authorization is required for the use of the Consent to Contact database.

Confirm that you will destroy the Protected Health Information (PHI) you and/or your Study Team acquire receive from JHS and/or UHealth at the earliest opportunity.
X ***I confirm***

Confirm that the Protected Health Inform (PHI) you acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.
X ***I confirm***

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).



_____7/31/26____
PI Signature Date

18) **Consent Process**

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

The protocol, key information form, informed consent form, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval prior to commencing with any study procedures. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously-consented participants need to be re-consented.

A waiver of documentation of consent is requested for the telephone pre-screening procedures described in the Recruitment section. This waiver applies to all prospective participants, irrespective of recruitment source, including individuals identified through existing TSCS Laboratory studies and research registries established by this team (ESSENTIAL, DORMIR, and MOSAIC; IRB ID 20210485, 20211142, and 20210569, respectively), individuals referred by treating physicians, individuals responding to flyers or advertisements, and individuals identified through the University of Miami Consent to Contact program. Pre-screening consists solely of collection of basic demographic information and administration of the QMCI and PAR-Q, involves no more than minimal risk, and includes no procedures for which written consent is normally required outside of a research context. Verbal permission will be obtained and documented by trained study personnel prior to initiating pre-screening. In addition, a partial waiver of HIPAA authorization is requested to permit trained, HIPAA-certified study personnel to access and review the limited protected health information necessary to identify and contact potentially eligible patients through the Consent to Contact program.

Written informed consent will be obtained at the in-person or virtual screening visit prior to any study procedures beyond pre-screening. Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant, and written documentation of informed consent is required prior to starting intervention. After signatures are obtained, each participant will be provided with a copy of the signed informed consent document.

Because this protocol enrolls individuals with mild cognitive impairment, capacity to provide informed consent will be assessed by trained study personnel at the time of consent. Participants must demonstrate understanding of the study purpose, procedures, risks, and voluntary nature of participation, and must be able to articulate that participation may be discontinued at any time without penalty. Individuals who do not demonstrate adequate capacity will not be enrolled; participants determined to have Alzheimer's disease or dementia based on QMCI performance are excluded from participation per the eligibility criteria. Referral by a treating physician confers no expectation of enrollment, and prospective participants will be informed that the decision to participate will not affect their clinical care.

The following consent materials are submitted with this protocol:

- Key Information Form
- Informed Consent Document

Informed Consent Document
Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. This study will be using in-person consent. Consenting procedure will proceed as follows:

- To ensure all eligibility criteria are met, prospective participants will initially be pre-screened via phone call, irrespective of recruitment source. Basic relevant demographic information (age, sex, education level, and whether the individual possesses and can use a smartphone/computer device), the Physical Activity Readiness Questionnaire, and the Quick Mild Cognitive Impairment screen (QMCI) will be used during screening to preliminarily exclude prospective participants. Age and education level are required to apply the age- and education-adjusted QMCI scoring thresholds. Verbal permission to proceed with pre-screening will be obtained and documented by trained study personnel prior to administration of any screening instrument. For individuals identified through the Consent to Contact program, study personnel will state at the outset of the call how the individual's contact information was obtained and that the individual previously agreed to be contacted about research opportunities.

- Those found to be eligible after an initial pre-screening call will be invited to come onsite or via a secure video conference call to have the study thoroughly explained to them, obtain consent, be randomized into one of three possible study arms (sleep, exercise, or sleep+exercise), and be oriented to the devices appropriate to the intervention to which each subject will be assigned. Participants will be given a copy of their signed consent. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The research assistant or postdoctoral fellow will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done for the study. The participants may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Prospective participants who were referred by a treating physician or identified through the Consent to Contact program will be explicitly informed that participation is entirely voluntary, that the decision to participate or decline will not affect their relationship with their treating physician or the care they receive within the University of Miami Health System, and that their treating physician will not be informed of their decision unless the participant wishes otherwise.
- A copy of the signed informed consent document will be stored in the subject's research record in REDCAP. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

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