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

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Study Title: Examining the effects of cognitive behavioral therapy for insomnia (CBT-I) on cognitive function and beta-amyloid in older adults (NCT03954210)

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

Lifestyle interventions to increase exercise and improve diet have been the focus of recent clinical trials to potentially prevent Alzheimer's disease (AD)[1,2]. However, despite the strong links between sleep disruptions, cognitive decline, and AD, sleep enhancement has yet to be targeted as a lifestyle intervention to prevent AD. A recent meta-analysis suggests that approximately 15% of AD may be prevented by an efficacious intervention aimed to reduce sleep disturbances and sleep disorders[3]. Chronic insomnia is the most frequent sleep disorder occurring in at least 40% of older adults[4]. Individuals with insomnia are more likely to be diagnosed with Alzheimer's Disease (AD)[5,6] and demonstrate decline in cognitive function[7] at long-term follow-up. AD is characterized by the accumulation of amyloid-β (Aβ) plaques and tau tangles in the brain, and growing evidence shows impaired sleep contributes to the accumulation of Aβ[8-10]. *An intervention aimed at improving insomnia may represent a critical opportunity for primary prevention to slow cognitive decline and potentially delay the onset of AD*. Cognitive behavioral therapy for insomnia (CBT-I) is an efficacious treatment for insomnia[11-14], but the use of CBT-I to improve cognitive function and potentially reduce the rate of Aβ accumulation has never been examined. Therefore, the long-term goal of this research agenda is to understand how addressing sleep disturbances may delay the onset of AD. The first step in this goal is to identify an efficacious intervention that impacts the modifiable risk of impaired sleep for developing AD. Therefore, the aims of this study are:

Aim 1: Examine the efficacy of CBT-I on improving cognitive function in older adults with symptoms of insomnia. CBT-I will improve speed of information processing (primary outcome), executive function, and episodic memory compared to a control condition at reassessment immediately following the interventions and at the 1 year follow-up.

Aim 2: Determine the association between change in sleep measures and change in cognitive function. Increased time spent in slow wave sleep (SWS) will be positively correlated with improvement in cognitive function in older adults with symptoms of insomnia. SWS is the critical period for removing Aβ from the brain of mice[10] and is associated with consolidation of declarative memory in humans[15].

Exploratory Aim: Examine the efficacy of CBT-I on reducing the rate of Aβ deposition in older adults with symptoms of insomnia. CBT-I will reduce the rate of Aβ deposition (measured using Florbetapir PET) compared to a control condition at the 1 year follow-up. Our primary amyloid burden measure will be mean change from baseline to 1 year in Florbetapir cortical-to-cerebellar ratio averaged across 6 regions of interest (frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus).

B. Background and Significance

The CDC considers poor sleep to be a public health problem due to the high prevalence and numerous health concerns that are associated with chronic poor sleep including an increased risk of developing AD[16].

Insomnia occurs in at least 40% of older adults[4]. People with insomnia[6] or sleep disturbances[17,18] had more than a 1.5-2.4 fold increase risk of developing AD at a 6-9 year follow up, and those who developed AD during that period and had insomnia had a faster cognitive decline than those without insomnia[6].

Aggregation of Aβ plaques is one of the pathological signs of AD. The accumulation of Aβ begins in the preclinical stage of AD,10-15 years before cognitive impairments are observed[8]. Accumulation of Aβ in the brain disrupts sleep, which then further exacerbates the accumulation of Aβ[8]. This bidirectional relationship between sleep disruption and Aβ accumulation may hasten the onset of AD. Recent research has demonstrated an association between poor sleep, Aβ deposition, and structural brain changes in humans[19,9]. This emerging evidence suggests that sleep disturbances and poor sleep quality likely contributes to changes in the brain that precipitate the onset of AD. No studies to date have examined if interventions aimed at improving sleep quality and reducing the effects of sleep disorders could delay the onset of AD.

Aβ is released into the interstitial fluid due to neuronal firing. During slow wave sleep, neurons are in a relatively silent state of hyperpolarization. Therefore, it is hypothesized that less Aβ is released during SWS compared to other more neuronally active periods of sleep[8]. Poor sleep quality and sleep fragmentation limits the time spent in SWS, which would result in increased time spent in lighter stages of sleep with increased neuronal firing and release of Aβ. Higher interstitial levels of Aβ are associated with earlier Aβ plaque formation[20] and higher levels of Aβ in the cerebrospinal fluid in cognitively normal older adults[21], which may hasten the onset of AD. Therefore, an intervention that increases SWS may reduce or delay Aβ deposition.

A meta-analysis shows that with aging there is a reduction in total sleep time, sleep efficiency, and slow wave sleep, while there is an increase in wake after sleep onset and sleep latency along with other sleep changes[22]. Along with the characteristic increase sleep latency, number of awakenings, and wake after sleep onset, individuals with insomnia spend less time in SWS[23,24] which may explain their increased risk of developing AD[6]. Cognitive behavioral therapy for insomnia (CBT-I) has been shown to increase SWS[25]. Therefore, this intervention may be a useful strategy to reduce the rate of Aβ deposition in people with insomnia.

C. Rationale

People with insomnia have increased risk of reduced cognitive function[7,26] and structural brain changes[27]. Furthermore, poor sleep quality[9,19] and reduced SWS[21] has been associated with increased Aβ deposition in cognitively normal adults. In addition, unpublished preliminary data suggests insomnia is associated with increased Aβ deposition. Therefore, this proposed study is significant because:

- Up to 40% of older adults experience chronic insomnia[4], and chronic insomnia has been shown to increase the risk of developing AD[6].
- Approximately 15% of AD may be prevented by an efficacious intervention aimed to reduce sleep disturbances and sleep disorders[3]
- CBT-I has been shown to have a medium to large effect on sleep outcomes in people with a variety of comorbid medical or psychiatric conditions[12,14] and is more effective long-term than pharmacological interventions[28].
- Therefore, the CBT-I intervention proposed in this study provides a critical opportunity for primary prevention to reduce the rate of Aβ deposition and potentially delay the onset of AD.

Addressing sleep disruption in people with AD is likely too late to have a significant impact on the progression of the disease. However, implementing an efficacious intervention to address insomnia is an innovative primary prevention strategy that could delay the onset of cognitive decline and AD. There is increasing interest in examining the role of sleep as a modifiable risk factor and a prevention target[29]. This proposed study is innovative because no prior studies have targeted sleep disturbances as a possible opportunity to impact the development of AD.

II. Research Plan and Design

A. Study Objectives: The objective of this study is to compare the efficacy of CBT-I on improving cognitive function in older adults with symptoms of insomnia and to assess the effect of CBT-I on rate of Aβ accumulation.

B. Study Type and Design: This proposed study is a randomized control trial of 6 weeks of CBT-I on cognitively normal (MMSE ≥25; AD8 < 3) individuals aged 60-85 years old (n=200). Individuals meeting the inclusion/exclusion criteria will be randomized to CBT-I (n=100) vs. control (n=100). Cognitive testing and polysomnography will be completed at baseline, immediately after intervention, and 1 year following intervention. A subset of n=50 participants will be randomly selected to participate in an optional Aβ accumulation substudy. The subset of participants will have Florbetapir PET and Magnetic Resonance Imaging (MRI) before and 1 year after the intervention.

C. Sample size, statistical methods, and power calculation

Sample Size Justification: Two hundred (n=200) individuals with symptoms of insomnia will be recruited to participate in this study. For this pilot study, a primary emphasis will be on effect size estimation as opposed to confirmatory hypothesis testing that typically follows this pilot study phase. Thus, as described below, 95% confidence intervals of effects will be estimated for each aim to support specific, future study design. With 200 subjects, and allowing for <20% attrition, we will have over 80 subjects per treatment arm remaining with complete data for analysis. This will enable estimation of effect sizes within approximately 0.31 standard deviations in magnitude for Aim 1 (assuming homogeneous variances across treatment groups), which proposes (below) a two-sample t-test approach, but we anticipate even greater precision as we propose (below) using linear mixed models for effect size estimation. For the Exploratory Aim, we anticipate 20 of the 25 subjects per treatment group will obtain both AB measures, which will allow for effect estimation within approximately 0.65 standard deviations in magnitude based on 95% confidence interval calculations. As there are multiple study measures, there is increased risk of multiplicity inflating type I errors. However, this is an initial study primarily aimed to estimate effect sizes for future confirmatory study. We will openly disclose this important fact when reporting our results in the literature. Thus, no further adjustments beyond our transparent disclosure will be conducted for our study.

Participants will be randomized using a randomization sequences generated by the study statistician (Phadnis). The study was designed based on CONSORT criteria[41] including concealed allocation for the project coordinator who will conduct screening and decide eligibility, random assignment, and independent, blinded intention-to-treat data analysis by the biostatistician.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

Table 1	
Inclusion Criteria	• 60-85 years old • report of difficulty falling asleep, maintaining sleep, or waking up too early at least 3 nights/week for the past 3 months • ≥10 on Insomnia Severity Index[43] • MMSE ≥ 25[32,33] and AD8 < 3[34]
Exclusion Criteria	• known untreated sleep disorder (such as sleep apnea or restless leg syndrome) • currently taking benzodiazepines, non-benzodiazepines, or melatonin supplements or agonists for insomnia

	• score of ≥15 on the Patient Health Questionnaire (PHQ-9) indicating severe depression or endorse any suicidal ideation (answer 1, 2 or 3 on #9 of the PHQ-9)[45] • History of drug or alcohol abuse as defined by DSM-IV criteria within the last 2 years • history of nervous system disorder such as stroke or Parkinson's disease • severe mental illness such as schizophrenia or bipolar disorder • history of developmental history of learning disability or attention-deficit/hyperactivity disorder • currently, or history of being, a shift worker • is currently receiving CBT-I treatment • unable to hear at a conversational level • failing a near vision test utilizing the Logarithmic Near Visual Acuity Chart (missing 3 or more letters on the 20/32 line or above) • Diagnosis of epilepsy

Participants will be requested to refrain from participating in other studies while participating in this study.

E. Specific methods and techniques used throughout the study

***Screening Procedures**:* Individuals will undergo a three steps screening process. The first portion will consist of a standard phone pre-screening. Those who meet the phone screening criteria will proceed to the second screening portion which will consist of a polysomnography to ensure the individual does not have a sleep disorder other than insomnia. Those without any other sleep disorder will be scheduled for an in-person MMSE to ensure the individual has no cognitive impairment.

Phone Pre-Screen:

1. Standardized review of inclusion/exclusion criteria (Table 1 above)
2. The Insomnia Severity Index (ISI)[42] which is a valid and reliable measure of sleep difficulties and consists of 7 questions each rated on a 0-4 scale. The range of scores on the ISI is 0-28, with ≥10 suggesting clinical insomnia[43].
3. Depressive symptoms will be assessed using the 9-item Patient Health Questionnaire (PHQ-9), with ≥15 suggesting moderately severe depression[45].
4. Cognitive status will be evaluated utilizing the AD8, eight item interview. Each item is evaluated with a "yes, there's a change," "no, theirs is not a change," and "N/A, don't know if there's a change" format. Individuals who indicate there have been 0-2 changes are considered to have normal cognition, whereas individuals indicating 3 or greater changes are likely to have cognitive impairment.

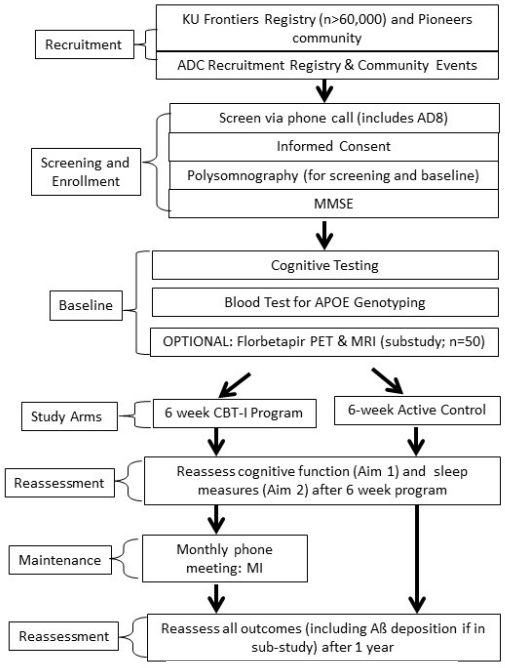

Figure 1. Study design.

Polysomnography: PSG will be conducted at either the KU Sleep Medicine Laboratory in the CTSU (which has 3 dedicated rooms for overnight polysomnography) or the Sleep Disorders Lab in TUKHS Pulmonary Function Department. Those who are diagnosed with a sleep disorder other than insomnia will be excluded from participating in the study. Those who do not have a sleep disorder other than insomnia will ideally be scheduled to complete baseline evaluation within two weeks, though a three-month window exists to

schedule a PSG. The PSG used for screening purposes will serve as the baseline assessment of slow wave sleep. The results of the PSG will not be shared with participants.

Mini Mental State Examination (MMSE):
A trained study staff member will administer the MMSE to screen out individuals without normal cognitive status. Those individuals who score an MMSE <25 will be excluded. Others who meet all inclusion and exclusion criteria will proceed to the enrollment process and baseline assessment. The MMSE will be conducted by the research assistant in the Sleep, Health, and Wellness Laboratory.

Near Vison Screen: a brief vision screen will be administered to ensure participants have adequate visual acuity to participate in the study. The Logarithmic Near Visual Acuity Chart will be used to assess near visual acuity. The chart will be placed on a wall and a measuring tape will be used to ensure the chart is 16 inches away from the participants eyes. Participants will be asked to read the letters on the chart. Participants missing 3 or more letters on the 20/32 (or higher) line will be excluded.

Baseline Evaluation: The baseline evaluation will consist of one visit to the Sleep, Health and Wellness Lab to perform the battery of cognitive tests and one visit to the KU CTSU for a blood draw for APOE genotyping. All participants will be asked to participate in the optional Aβ accumulation substudy. Participants who participate in the sub-study will undergo Florbetapir PET at KU Nuclear Medicine at the Overland Park location and an MRI at the Hoglund Brain Imaging Center within two weeks of screening.

Battery of cognitive tests: Cognitive testing will take place at the in a quiet room with a trained research assistant. The cognitive function domains of speed of information processing, memory, and executive function will be assessed by a battery of valid and reliable measures. Counterbalanced alternate forms of the cognitive function tests will be used. The assessors will be blinded to participant group assignment. The battery of cognitive tests is anticipated to take 1.5 hours to complete. The results of the cognitive tests will not be shared with participants.

Speed of Information Processing

1. The Continuous Performance Test (CPT) requires participants to respond as quickly and accurately as possible to a series of stimuli that are delivered via computer. The participants will be instructed to tap the space bar for every letter except “X.” The participants scores will be determined by their scores in detectability (e.g., difficulty differentiating targets from non-targets), error type (e.g., omissions, commissions, perseverations) and reaction time statistics.

Memory

1. For the The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a series of eleven tests that require the participant to remember and recall information, as well as copy figures and provide semantically related information to a stimulus. The total number of correct items the participant achieves in each subtest is calculated into an index score for the following skills: immediate memory, visuospatial/constructional, language, attention and delayed memory.

Executive Function

1.The Stroop Test[60] requires participants to inhibit the natural response (reading a word) and replace it with another response (saying a color). Each participant is given a list of X’s printed in colored ink and a list of words printed in colored ink. The participant is instructed to name the color of the ink. They are given 45 seconds to name as many colors as they can. The reported outcome measure of this test is an interference score that is the difference between the two conditions while normalizing for number of x’s using the following formulae: x-words/x.

2. For Backward Digit Span, participants are told a line of numbers and required to accurately recall them in the reverse order from which they were told. A participant's total score is calculated by the total number of numerical strings the participant correctly recalled.

Motor Skills

1. the Grooved Pegboard test requires participants to place pegs into a pegboard utilizing one hand at a time as quickly as they can. The first trial is done with their dominant hand, while the second trial is done with their non-dominant hand. A participant's score is determined by how long it took them to complete the trial with their dominant and non-dominant hand. The number of pegs that were left unplaced, or that were dropped, is also recorded.

Motivation

1. The Coin in Hand is a brief test of motivation to ensure participants are giving full effort during testing. The test requires them to remember in which of two hands the examiner has held a coin. After showing the coin for about two seconds in one hand, participants are required to close their eyes and count backward from 10. They are then asked to indicate in which of the two clenched hands the coin is held. The examiner then opens the hand touched by the participant and gives verbal feedback as to the correctness of the subject's response. Ten trials are given, with the coin being held in the right hand and left hand for an equal number of randomly distributed trials. The total score is the number of times the participant guessed which hand the coin was in correctly. Malingering individuals will perform at about a chance level (.50).

Other Psychosocial Measures*:* Due to their known association with cognitive function or their possible role as mediator of effectiveness of the CBT-I intervention, depression, anxiety, sleep self-efficacy, and motivation to change sleep behavior will also be assessed.

1. Patient Health Questionnaire (PHQ-9)[45] to assess depression during the past 2 weeks. It consists of 9 items with a score ranging from 0-27. A tenth question that is not included in the summary score assesses how depressive symptoms affect functional level. The PHQ-9 will be used as a screening tool and also an outcome measure.
2. Generalized Anxiety Disorder Assessment (GAD-7)[62] to assess anxiety over the past 2 weeks. This questionnaire consists of 7 items, and the score from each item is summed for an overall score ranging from 0-21 with a higher score indicated a higher level of anxiety. An additional eighth question assesses if anxiety impact daily activities and sociability.
3. Sleep Efficacy Scale (SES)[63] to assess level of confidence in being able to implement behaviors that are helpful to promote sleep. This scale includes 9-items that are scored on a 4-point scale (1-5). The total scores range from 9–45 with a higher score indicating higher self-efficacy.
4. Motivation to Change Sleep Behaviors: Will be assessed using the question "How motivated are you to change your current sleep behavior?" rated on a 5-point Likert scale with 0 being not at all motivated to 4 being very motivated

APOE genotyping: A trained phlebotomist will draw blood (20ml) into Acid Citrate Dextrose Vacutainer tubes for genomic DNA extraction. APOE genotyping will be completed by an outside reference laboratory (Polymorphic DNA) using restriction enzyme isotoping. The results of genotyping will not be shared with participants.

Florbetapir PET: Florbetapir PET images will be obtained on a GE Discovery ST-16 PET/CT scanner in the Nuclear Medicine department. Subjects will have a catheter placed for IV administration of Florbetapir F 18 Injection. Vital signs will be taken in a supine position immediately prior to administration of Florbetapir (within 5 minutes). Subjects will receive a single IV bolus of Florbetapir (370 MBq) followed by 2 brain PET frames of 5 minutes duration acquired continuously, approximately 50 minutes post-dose injection. Frames are reconstructed to a single PET image in native space. Adverse events will be continuously monitored

during the imaging session, and participants will have follow-up phone call within 2 business days after the imaging session to confirm patient well-being and to collect information about any new adverse events. The results of the PET scan will not be shared with participants.

Magnetic Resonance imaging (MRI): A structural ADNI MPRAGE scan will be conducted for alignment/region of interest analysis of PET Data. All MRI scans will be conducted at the Hoglund Brain Imaging Center (HBIC) and will be scheduled by the study coordinator at the same time PET imaging is scheduled (though the two events will likely not occur on the same day).

Interventions:

Cognitive Behavioral Therapy for Insomnia (CBT-I): The CBT-I program is a 6-week in-person one-one-one program with a graduate research assistant in a psychology program who is trained in providing CBT-I. Under extenuating circumstances, participants may be asked to participate in CBT-I remotely over a secure teleconference app or phone. A standardized CBT-I program will be used.[50] Participants will maintain a sleep diary during the course of the program to aid in tailoring the program. Each session will begin with a summary and graphing of sleep diary data and will include an assessment of treatment gains and adherence. The general sessions outlines are as follows with each session lasting 45-60min:

Session 1: determine treatment plan, set up sleep schedule and stimulus control, discuss strategies for how to stay awake to prescribed hour and what to do if wake up in middle of night, sleep hygiene education
Session 2: continue upward titration of total sleep time, review sleep hygiene; introduce diaphragmatic breathing
Session 3: continue upward titration of total sleep time, introduce mindfulness
Session 4: continue upward titration of total sleep time, introduce progressive muscle relaxation
Session 5: continue upward titration of total sleep time, discuss negative sleep beliefs
Session 6: assess global treatment gains, discuss relapse prevention

Following completion of the CBT-I program at 6 weeks until the 1 year follow-up session, participants will have a monthly phone meeting (or email if requested by participant) with research personnel to discuss maintenance of the strategies learned during the program and problem-solve strategies if needed.

Active Control Group: Participants randomized into the Active Control (AC) group will attend 6 weekly 45-60 min sessions that include gentle stretching activities for major muscle groups accompanied by lifestyle education with a graduate research assistant to control for socialization and contact with research personnel. Under extenuating circumstances, participants may be asked to complete AC visits remotely over a secure teleconference app or phone.

Session 1: Basic sleep education, stretching exercises
Session 2: Sleep hygiene education (environmental factors & sleep positions), stretching exercises
Session 3: Sleep hygiene education (lifestyle factors), stretching exercises
Session 4: Diet recommendations, stretching exercises
Session 5: Exercises recommendations, stretching exercises
Session 6: Discus maintaining achievements & preventing relapses, stretching exercises

Reassessment: Participants will undergo reassessment of cognitive function and slow wave sleep via PSG within 1-2 weeks following completion of the 6-week CBT-I intervention or control condition and again at 1 year. Those participating in the sub-study will undergo Florbetapir PET and MRI at 1 year only. Under extenuating circumstances, participants may be asked to complete reassessment questionnaires remotely through a secure online survey and cognitive testing over a secure teleconference app. In this case, cognitive testing sessions will be recorded and saved on a secure network drive at KUMC.

Reassessment results will not be shared with participants.

F. Risk/benefit assessment: There may be other risks of the study that are not yet known.

1. Physical risk:

i. CBT-I: A risk of participating in a CBT-I intervention is the participant may become more sleepy initially which may impact their fatigue, thinking ability, and functional abilities. It is anticipated that this increase in sleepiness will be temporary and should help them sleep better in the long term. If a significant increase in sleepiness occurs, the intervention may need to be modified for the participant.

ii. Active control: A risk of participating in the active control group is muscle soreness from stretching and light activity and potentially falling if balance is lost during these activities. All activities are supervised by research personnel to reduce these risks.

iii. Polysomnography: A risk of participating in PSG is difficulty sleeping and possible fatigue and frustration with this difficulty sleeping. If the participant becomes frustrated at any time during sleep recording and wishes to stop the study (due to frustration or fatigue with difficulty sleep or for other reasons), the researcher will stop testing.

iv. APOE genotyping: Risks of venipuncture to determine APOE genotype is minor bruising, discomfort or pain with the needle stick, feelings of anxiety or discomfort, feeling faint or fainting. A trained phlebotomist will perform the procedure to lessen the risk.

v. PET: Risks of PET imaging are allergic reaction to the radioactive drug, exposure to radiation, same risks of venipuncture as above, headache, injection site reactions, musculoskeletal pain, nausea, fatigue, back pain, anxiety/claustrophobia, insomnia, hypertension, and neck pain.

vi. MRI: Risks of MRI include any metal (e.g., artificial joints, heart valves, insulin pumps, etc.) within the body being moved by the strong magnet within the MRI apparatus if the participant did not notify appropriate personnel. Anxiety/claustrophobia are potential risks as well.

2. Psychological risks:

i. Cognitive testing: During completion of the cognitive tests, participants become frustrated or fatigued. If this happens, they are allowed to stop if needed. Also, participants might be embarrassed by some of the questions on the questionnaires. They are free not to answer any questions. The data collection will be described in detail to the subjects at the time of consent. Subjects will have an opportunity to ask for clarification on any study tasks. Subjects will be instructed that they have the authority to stop the testing at any point should they feel uncomfortable with the protocol.

ii. CBT-I: Participants may get frustrated or anxious if their sleep becomes initially worse, which occasionally happens at the beginning of CBT-I. They will be reassured and emphasis during sessions will include relaxation techniques and other cognitive strategies. They may also become frustrated if they do not experience an improvement in sleep.

iii. Active control: Participant may get frustrated or anxious if they suspect they are in the control condition or if they do not experience an improvement in sleep.

iv. Polysomnography: see above under “physical risks”

v. APOE genotyping: see above under “physical risks”. Participants will not be given the results of the test, so participants may be frustrated at not receiving the results. While APOE4 disclosure is safe under appropriate conditions, the memory clinic does not routinely disclose because medical advice does not differ based on APOE status.

vi. PET: see above under “physical risks”

vii. MRI: See above under “physical risks”

3. **Economic risks**: none anticipated
4. **Social risks**: none anticipated
5. **Legal risks**: In case of any injury or illness resulting directly due to participation in the study, the subject will not give up any legal rights even if he/she signs the consent form

6. **Potential benefit of participating in the study**: If randomized into the CBT-I group, the participant may benefit from improved sleep and may benefit from improved health outcomes that have been shown to occur with improved sleep. In addition, researchers hope that the information from this research study may be useful in the treatment of older adults with insomnia and potentially reduce the rate of beta-amyloid accumulation which may lessen the risk of developing Alzheimer’s Disease.

G. Location where study will be performed:

1. Consent Process: at participant’s home for Consent 1 with support from research personnel as needed; quiet private room in Sleep, Health and Wellness Lab for Consent 2

2. Cognitive testing, other questionnaires: quiet private room in Sleep, Health & Wellness Lab, or remotely (online questionnaires and testing over teleconference) under extenuating circumstances

3. Blood draw for genotyping: CTSU

4. Polysomnography**:** KU Sleep Medicine Laboratory within the CTSU

5. PET Imaging: KU Nuclear Medicine department at Overland Park location

6. MRI Scan: Hoglund Brain Imaging Center

7. CBT-I and Active Control: Sleep, Health and Wellness Laboratory (Siengsukon’s lab)

H. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s):
    a. Consent Process: study coordinator, research assistant
    b. Cognitive testing and other questionnaires: trained research assistant
    c. Blood draw for genotyping: trained phlebotomist
    d. Polysomnography: sleep medicine physician, sleep lab technicians
    e. PET Imaging: nurse, technician
    f. MRI: nurse, technician
    g. CBT-I and Active Control: Siengsukon, research assistants
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: study coordinator
    b. Obtaining informed consent: study coordinator and research assistant
    c. Providing on-going information to the study sponsor and the IRB: study coordinator
    d. Maintaining participant's research records: study coordinator
    e. Completing physical examination: N/A

f. Taking vital signs, height, weight: N/A
g. Drawing / collecting laboratory specimens: trained phlebotomist
h. Performing / conducting tests, procedures, interventions, questionnaires: trained research assistants
i. Completing study data forms: depends on forms, see above
j. Managing study database: study coordinator

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

Research personnel will continually monitor participants for adverse events. Any adverse event will be immediately reported to the PI and study coordinator and the Human Subjects Committee per KUMC Human Subject Committee reporting policies. The ADC has a series of ongoing clinical trials and a team of experts in running clinical trials. One of the physicians associated with the ADC will serve as the Independent Safety Monitor who will be asked to quarterly to review adverse events and the overall safety of the ongoing trial.

Should a study participant experience an adverse event in any category rated 3 or greater according to CTCAE v3.0, that individual will be removed from the study immediately. Should more than 10% of participants in a study arm experience adverse events during the study period in any category rated 3 or greater according to CTCAE v3.0, the study will be terminated immediately.

Reporting: All AEs will be reported quarterly to the Independent Safety Monitor. The summary of all other AEs will be reported to NIH Program Administrator and to the safety officers quarterly. Unanticipated SAEs related to the intervention (or testing) will be reported to the Independent Safety Monitor and NIH Program Administrator within 48 hours of the knowledge of the SAE. Deaths will be reported to the IRB, NIH Program Administrator, and to the safety officers within 24 hours of our knowledge of the death.

III. Subject Participation

A. Recruitment: Participants will be recruited from the Heron Data Repository/Pioneers Participant Registry, physician groups, media outlets, social media, and the community, including KU Alzheimer's Disease Center (KU ADC) community-outreach events and registry. The study will also be listed on clinicaltrials.gov. A preliminary search within the Frontiers Participant Registry indicated 1,315 individuals would meet the inclusion/exclusion criteria, have agreed to be contacted for participation in research studies, and live within a 20 mile radius of KUMC. The KU Alzheimer's Disease Center (KU ADC) has a Core dedicated to recruitment and initial screening of potential study participants. The Outreach and Recruitment Core hosts over 75 community events per year education approximately 1000 individuals, while encouraging them to participate in clinical research. A dedicated physician liaison supports research referrals from regional geriatric practices. Dedicated staff-led Latino and African-American outreach programs. Two Research Recruitments Specialists and a contracted call center receive over 100 calls per month, screening individuals for ongoing trials. Near real-time metrics regarding referral source, response to trial marketing, and trial enrollment provide enhanced efficiency over older models of participant recruitment.

B. Screening Interview/questionnaire: The screening interview will be conducted by phone by the study coordinator. The phone screen consists of:

1. Standardized review of inclusion/exclusion criteria (Table 1)

2. The Insomnia Severity Index (ISI)[42] which is a valid and reliable measure of sleep difficulties and consists of 7 questions each rated on a 0-4 scale. The range of scores on the ISI is 0-28, with ≥10 suggesting clinical insomnia[43].
3. Depressive symptoms will be assessed using the 9-item Patient Health Questionnaire (PHQ-9), with ≥15 suggesting moderately severe depression[45].
4. Cognitive status will be assessed utilizing the AD8, eight item interview. Each item is evaluated with a "yes, there's a change," "no, theirs is not a change," and "N/A, don't know if there's a change" format. Individuals who indicate there have been 0-2 changes are considered to have normal cognition, whereas individuals indicating 3 or greater changes are at increased risk of having cognitive impairment. A score of 3 or greater has slightly lower sensitivity than cut off of 2 (90% vs 92% respectively) but has higher specificity (68% vs 46% respectively).

C. Informed consent process and timing of obtaining of consent

Informed consent will consist of a two-part process. The first consent process will occur prior the participant undergoing the polysomnography. The language in this consent form will include consent to the screening assessments (polysomnography, MMSE, and near vision) as well as possibility for exclusion from the study based on PSG, MMSE, or near vision results. This consent form will be available in electronic format that the participant will read and sign prior to the PSG (they will be emailed a copy on REDCap; a paper copy version will be mailed if they do not have email access and will be available at the KU Sleep Medicine Laboratory if they didn't complete prior to arrival). The study coordinator will explain this consent form over the phone following phone pre-screening.

The second informed consent will precede official study enrollment (prior to baseline assessments). Informed consent will be administered by the research assistant and electronically signed in REDCap. A copy will be immediately provided to the participant. Individuals will be given as much time as they want to read over and ask questions about participation during the consent process. During this time, participants will also be asked to participate in the optional Aβ accumulation sub-study involving PET scans and will sign the optional portion of the consent form.

D. Alternatives to Participation: The alternative to participation is to not participate.

E. Costs to Subjects: There are no costs to the individuals for participating

F. How new information will be conveyed to the study subject and how it will be documented: Participants will be told about anything new that might change their decision to be in this study. They will be asked to sign a new consent form if this occurs.

G. Payment, including a prorated plan for payment: Participants will be paid $100 for completing baseline assessment, $100 for completing the immediate post-intervention assessment, and $150 for completing the 1 year assessment. Individuals who participate in the PET/MRI sub-study will receive an additional $50 at baseline and after completing the 1 year imaging follow-up.

IV. Data Collection and Protection

Data Management and Security: Study data will be collected and managed using the Research Electronic Data Capture (REDCap) web-based, electronic data capture tools hosted on a secure, HIPAA

compliant server at KUMC.[70] REDCap provides validated data entry and audit trails. All data will be collected on standard source documents and entered into standard case report forms in REDCap. These forms have been developed and are currently in use to support data collection for ongoing interventions and to support the KU ADC clinical and cognitive evaluations. Forms include paper and electronic source documents for outcome and clinical assessments. The Division of Medical Informatics ensures data security by managing all data on a secure server that has role-based access that is password protected. All files that are modified are backed up daily, with complete backups of the server on a weekly basis. All data are stored in a HIPAA compliant manner.

Only IRB-approved research personnel will have access to data. Any paper documents will be stored in a locked file cabinet in the Sleep, Health and Wellness Laboratory (Siengsukon's lab). Any data downloaded from REDCap will be stored on the KUMC network-supported P drive. Participants will be given a study ID so only their study ID will be linked to their data. The study coordinator and the PI will have access to the key to the study IDs.

V. Data Analysis and Reporting

A. Statistical and Data Analysis:

Statistical Analysis for Aim 1: We hypothesize CBT-I will improve speed of information processing (primary outcome), executive function, and episodic memory compared to a control condition at reassessment immediately following the interventions and at the 1 year follow-up. As this is a randomized study, we anticipate that measured and unmeasured confounding variables will be balanced between groups. Consequently, an intent-to-treat (ITT) approach will be used for the primary analyses. The Aim 1 outcome measures are relatively continuous; thus, our approach will be to model using linear mixed models (LMMs) to account for dependence between observations collected on the same subject over time for all measures. We will allow for a random intercept for each subject to account for this dependence. Measures will be collected at baseline, following the 6-week intervention, and at 1-year follow-up. We will first build and assess our LMMs without adjustment as well as with adjustment for any unbalanced, measured covariates as a secondary analysis. We will conduct residual analyses, including predicted versus residuals, quantile-quantile plots, and residual (conditional and unconditional) histograms. Alternate models, e.g., generalized linear mixed models, will be utilized instead to identify better model fits to the data. Once models are generated, we will conduct (two degree-of-freedom) tests for differences between groups in modeled change in cognitive function measures from baseline to immediate post-intervention period and after one year. This approach tests the null hypothesis that the mean group difference at baseline is zero and (simultaneously) the mean group difference at one year follow-up is zero to serve as a gatekeeping approach. If indicated as significant, we will assess change from baseline of each time point individually for differences between groups using single degree-of-freedom linear contrasts. In the event of unbalance between groups in baseline measures is detected, we will conduct secondary analyses (following conduct of primary ITT analyses) that are adjusted for factors that appear unbalanced. This secondary, adjusted analysis will also include—regardless of statistical significance—the APOE4 genotype, age, sex, education, and a model that includes an interaction of our treatment factor with APOE4 genotype. This enhancement to the statistical plan is due to these covariates having previously been implicated as a response modifier in previous studies. Linear contrast combinations of model parameters will be used based on the LMMs which will provide estimates of the effect sizes for various measures used in this study.

Statistical Analyses for Aim 2: We hypothesize more time spent in slow wave sleep (SWS) will be positively correlated with improvement in cognitive in older adults with symptoms of insomnia. For Aim 2, we will first assess these mechanistic hypotheses using LMMs. We will use longitudinal measures of sleep and correlate the with cognitive function models, with cognitive function (over time) being the outcome. Model assessment will follow a similar strategy to that described for Aim 1. Testing the parameters of sleep measures covariate effects will facilitate the assessment of the research hypothesis that increased time spent in slow wave sleep (SWS) following CBT-I will be positively correlated with improvement in cognitive function in older adults with symptoms of insomnia. Since there are only two AB measures, we will use

linear regression to predict change in AB burden as a function of change in sleep measures from both baseline to immediate post-intervention and post-intervention to 1-year follow-up. Similar residual analyses to those described for Aim 1 of this linear model will be conducted. In order to facilitate an ITT comparison for this subset, we will randomly sample subjects for participation in this study by randomly identifying a subset for recruitment into the study as a participant for inclusion in this aim in the randomization schedule.

Statistical Analyses for Exploratory Aim: We hypothesize CBT-I will reduce the rate of Aβ deposition (measured using Florbetapir PET and MRI) compared to a control condition at the 1 year follow-up. Our primary amyloid burden measure will be mean change from baseline to 1 year in Florbetapir cortical-to-cerebellar ratio averaged across 6 regions of interest (frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus). For this Exploratory Aim, we will compare the changes from baseline to 1-year follow-up in AB measures between groups. This is the two-sample paired t-test, or equivalently the two-sample t-test of the change scores. Using the latter approach as the primary analysis for this study, we can conduct analogous inference if indicated by residual analyses (quantile-quantile plots, residual histograms, etc.) using the Wilcoxon rank-sum test of the change scores. We can also extend this approach for secondary analyses with adjustment for unbalanced factors using linear models (i.e., ordinary least squares regression). Specifically, we will also conduct a secondary test that controls for SWS and for amyloid burden, both measured at baseline. The focus will be on effect size estimation as opposed to power for a definitive test. Thus, we will utilize the analogous formulas to estimate two-sided, 95% confidence intervals either from the parametric or nonparametric approaches we described above. Even in light of potentially slower than expected accumulation differences between groups, we believe this estimation approach to this aim will be extremely beneficial to enhancing our understanding of the relationship between CBT-I and amyloid accumulation.

B. Expected Outcome:
Aim 1: CBT-I will improve speed of information processing (primary outcome), executive function, and episodic memory compared to a control condition at reassessment immediately following the interventions and at the 1 year follow-up.

Aim 2: Increased time spent in slow wave sleep (SWS) will be positively correlated with improvement in cognitive function in older adults with symptoms of insomnia. SWS is the critical period for removing Aβ from the brain of mice[10] and is associated with consolidation of declarative memory in humans[16].

Exploratory Aim: CBT-I will reduce the rate of Aβ deposition (measured using Florbetapir PET and MRI) compared to a control condition at the 1 year follow-up. Our primary amyloid burden measure will be mean change from baseline to 1 year in Florbetapir cortical-to-cerebellar ratio averaged across 6 regions of interest (frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus).

C. Study results to participants: Study results will not be given to participants

D. Publication Plan: Research results will be published in peer-reviewed journals and disseminated via presentations at conferences and professional meetings.

VI. Bibliography / References / Literature Cited

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