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Cognitive behavioral therapy for insomnia to enhance cognitive function and reduce the rate of Aβ deposition in older adults with symptoms of insomnia: A single-site randomized pilot clinical trial protocol

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ABSTRACT

Lifestyle interventions to increase exercise and improve diet have been the focus of recent clinical trials to potentially prevent Alzheimer's disease (AD). 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. Chronic insomnia is the most frequent sleep disorder occurring in at least 40% of older adults. Individuals with insomnia are more likely to be diagnosed with Alzheimer's Disease (AD) and demonstrate decline in cognitive function 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. An intervention aimed at improving insomnia may be 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, but the use of CBT-I to improve cognitive function and potentially reduce the rate of Aβ accumulation has never been examined. Therefore, the objective of the proposed study is to examine the efficacy of CBT-I on improving cognitive function in older adults with symptoms of insomnia. An exploratory aim is to assess the effect of CBT-I on rate of Aβ accumulation.

1. Introduction

Insomnia occurs in at least 40% of older adults [2]. People with insomnia [3] or sleep disturbances [12,13] had more than a 1.5–2.4 fold increase risk of developing Alzheimer's Disease (AD) at a 6–9 year follow up, and those who developed AD during that period and had insomnia, demonstrated faster cognitive decline than those without insomnia [3]. Interventions aimed at improving insomnia are a critical opportunity for primary prevention to delay the onset of AD.

Insomnia is associated with an increased risk of cognitive decline [14] and structural brain changes, including reduced bilateral hippocampal volume compared to those without insomnia [15–18]. Furthermore, atrophy in the hippocampus is associated with decline in cognitive function often experienced by individuals with chronic insomnia [18,19]. Therefore, it is conceivable that using a known efficacious intervention to effectively treat insomnia prior to the onset of cognitive changes may be a primary prevention strategy to delay the onset of AD.

Aggregation of Aβ plaques is one of the pathological signs of AD. The accumulation of amyloid-β (Aβ) begins in the preclinical stage of

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AD,10–15 years before cognitive impairments are observed [5]. Accumulation of Aβ in the brain disrupts sleep, which then further exacerbates the accumulation of Aβ [5]. This bidirectional relationship between sleep disruption and Aβ accumulation may hasten the onset of AD [20–22]. Recent research has demonstrated an association between poor sleep, Aβ deposition, and structural brain changes in humans [6]. In particular, slow wave activity has been associated with higher cortical Aβ burden [23,24]. Cerebrospinal fluid movement has been shown to be increased during slow wave sleep [7,25] which may aid the clearance of Aβ. Therefore, an intervention that increases slow wave sleep (SWS) may reduce or delay Aβ deposition.

Cognitive behavioral therapy for insomnia (CBT-I) is an effective treatment for insomnia [8,10]. CBT-I is more effective long-term for treating insomnia than pharmacological interventions [26]. In addition, two recent meta-analyses [9,11] determined CBT-I produced medium to large effect sizes on sleep outcomes in people with a variety of comorbid medical or psychiatric conditions. Importantly, improvements in sleep outcomes remain for up to at least 10 years following the intervention [27]. However, the efficacy of CBT-I to improve cognitive function or alter Aβ deposition has never been examined.

Therefore, the aims of this randomized clinical trial are:

Aim 1: Examine the efficacy of CBT-I on improving cognitive function in older adults with symptoms of insomnia. 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.

Aim 2: Determine the association between change in sleep measures and change in cognitive function. We hypothesize an increased time spent in slow wave sleep (SWS) will be positively correlated with improvement in cognitive function in older adults with symptoms of insomnia.

Exploratory Aim: Examine the efficacy of CBT-I on reducing the rate of Aβ deposition in older adults with symptoms of insomnia. We hypothesize CBT-I will reduce the rate of Aβ deposition (measured using Florbetapir

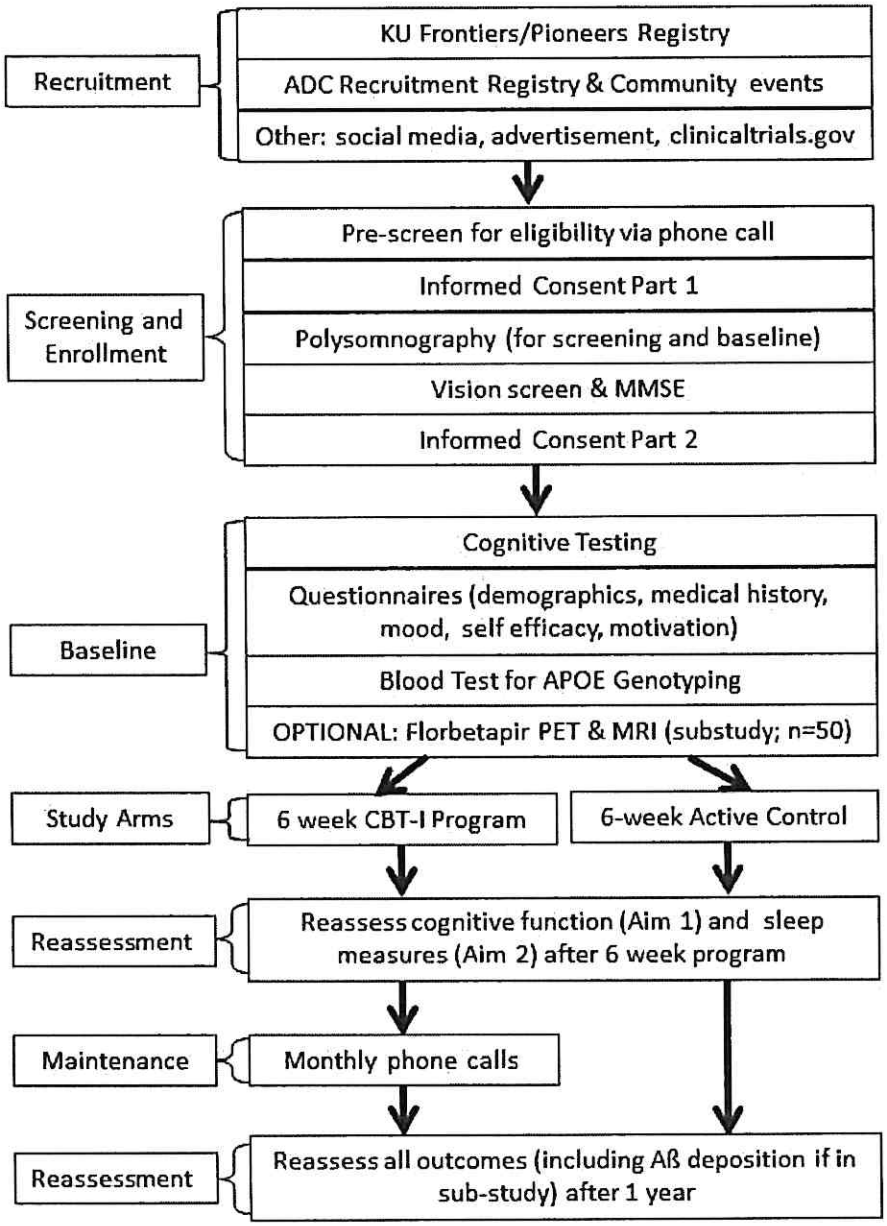

Fig. 1. Study design.

PET) compared to a control condition at the 1-year follow-up.

2. Study overview

This proposed study is a randomized control trial of 6 weeks of CBT-I on cognitively normal (MMSE $\geq$ 25 [29,30] and AD8 < 2 [31]) 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) using randomization sequences generated by the study statistician. The study was designed based on CONSORT criteria [28] 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. Cognitive testing and polysomnography will be completed at baseline, following 6-week intervention, and at 1 year. A subset of n = 50 participants will be invited to participate in an optional Aβ accumulation substudy on a rolling basis. The subset of participants will have Florbetapir PET and MRI before and 1 year after the CBT-I intervention or control condition. Fig. 1 provides an overview of the screening and study events described in more detail below.

3. Recruitment, enrollment and randomization

3.1. Recruitment

Participants will be recruited through the KUMC Heron Data Repository/Pioneers Participant Registry, the KUMC PIONEERS Community Registry, physician groups, media outlets (i.e., local newspaper), social media, recruitment resources (i.e., ResearchMatch.org), and the community (i.e., local YMCA's, independent living communities, libraries, etc.), and community-outreach events and registry. The study is also listed on clinicaltrials.gov (#NCT03954210).

3.2. Screening procedures

Individuals will undergo a three-step screening process. The first portion will consist of a standardized phone prescreening to determine if the individual meets the inclusion/exclusion criteria (Table 1).

Those who meet the phone screening criteria will proceed to the second screening portion which will consist of polysomnography (PSG) to ensure the individual does not have a sleep disorder other than insomnia. Those who do not have a sleep disorder other than insomnia (excluded if AHI > 14/h or PLM > 14/h or any other sleep disorder reported by neurologist board-certified in sleep medicine) will then undergo MMSE and near vision test. Individuals who incorrectly identify three or more letters on the 20/63 line or any line above the 20/63 line on the Logarithmic Near Visual Acuity Chart (Good-Lite, Elgin, IL) or who score an MMSE < 25 [29,30] will be excluded. Individuals who pass the third screening process will be enrolled in the study and undergo baseline assessment at the same visit.

Table 1
Inclusion and Exclusion Criteria.

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 [29] • MMSE ≥ 25 [29,30] and AD8 < 2 [31]
Exclusion criteria	• known untreated sleep disorder (such as sleep apnea or restless leg syndrome) • Apnea Hypopnea Index > 14/h or Passive Limb Movements > 14/h • 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) [30] • 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 • developmental history of learning disability or attention-deficit/hyperactivity disorder • currently or history of being a shift worker • is currently receiving or has received 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

3.3. Randomization

Following baseline assessment, participants will be randomized to CBT-I (n = 100) vs. control (n = 100). A randomization list developed by the study statistician will be used. The randomization program code was written in SAS to derive this list and will be maintained by one unblinded study staff member. Study staff performing the baseline assessments and reassessments will be blinded to the participant's intervention arm (CBT-I vs. control). Blinding participants to which group they are randomized into is not possible as the intervention arms are obviously different.

4. Assessments

The baseline evaluation will consist of gathering demographic information, a battery of cognitive tests, and psychosocial questionnaires. The PSG used for screening purposes will serve as the baseline assessment of slow wave sleep for Aim 2 and will be completed again following the intervention and 1 year later. Participants will undergo a blood draw for APOE genotyping. Individuals who enroll in the substudy will undergo MRI and Florbetapir PET imaging to examine the efficacy of CBT-I on reducing the rate of Aβ deposition at baseline and at the 1-year reassessment.

4.1. Demographics

Demographic data will be collected on all participants during their baseline assessment visit. The following demographic data will be collected: age, education level, race/ethnicity, marital status, gender, employment status, medical history, and smoking/alcohol status. Follow-up questionnaires at 6-week and one-year will collect information on any changes in medical history (i.e., updates in medical events/medications) and smoking/alcohol status.

4.2. Battery of cognitive tests

The cognitive function domains of speed of information processing, memory, and executive function will be assessed by a battery of valid and reliable measures (Table 2). Counterbalanced alternate forms of the cognitive function tests will be used except for the NAB Digit Forwards/Digits Backwards Test (which has two test forms) and the Stroop Test (which has one test form). The assessors will be blinded to participant group assignment. The battery of cognitive tests will be done at baseline, following the intervention, and 1-year later.

4.3. Speed of information processing (primary outcome)

1. For the Continuous Performance Test (CPT) [31], participants sit in front of a laptop computer and watch a screen that presents one letter at a time. Participants are instructed to press the spacebar as quickly as possible for every presented letter with the exception of the letter X. The primary outcome measures are hit reaction time (HRT) and HRT standard deviation (HRT SD).

Table 2
Outcomes for Aim 1.

Primary domains assessed	Outcomes
Cognitive Function	
Speed of Information Processing	Continuous Performance Test (CPT) [31] Coding Test (RBANS Versions) [32]
Memory	RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) [32]
Executive function	Stroop Test [33] NAB Digits Forward, Digits Backward [34]
Secondary domains assessed	
Depression	Patient Health Questionnaire (PHQ-9) [30]
Anxiety	Generalized Anxiety Disorder Assessment (GAD-7) [35]
Sleep self-efficacy	Sleep Efficacy Scale (SES) [36]
Motivation to change behavior	Motivation to Change Sleep Behaviors 5-point Likert scale

2. For the Coding Test [32], a series of symbols will be placed in front of the participant with a key at the top of the page. The participants will be instructed to use the key to quickly write the number that matches the corresponding symbol. The total number of correct responses in 90 s will be used as the outcome measure.

4.4. Memory

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [32] is a set of twelve tests that produce the following index scores: immediate memory, visuospatial/constructional, language, attention, and delayed memory skills. The primary outcome will be performance on the immediate memory and delayed memory indices.

4.5. Executive function

1. For the Stroop Test (Golden) [33], the participant is given a list of X's printed in colored ink (red, blue, green or tan) in trial 1, and in trial 2 the participant is given a list of color words printed in different colored ink (e.g., the word "red" printed in green ink). In both trials, participants are instructed to name the color of the ink. They are given 45 s to read as many stimuli as they can. The reported outcome measure of this test is an interference score that is the difference between the predicted color-word score (based on the raw word score and raw color score) and raw color-word score.
2. The Neuropsychological Assessment Battery Digits Forward/Digits Backward Test [34] requires participants to remember and recall strings of numbers ranging from three to nine digits. Participants are first required to do this recalling the numbers in a forward direction (i.e., the same order they are presented by the examiner), and then in a backward direction (i.e., the reverse order presented by the examiner). The primary outcome is the number of trials the participant accurately recalled in the forward direction and the backward direction.

Because motor performance and motivation may impact performance on the cognitive tests, motor performance will be assessed using the *Grooved Pegboard* (Lafayette Instrument Company,® Lafayette, IN), and the *Coin In the Hand Test* [37] will be used to assess participants motivation.

4.6. 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 (Patient Health Questionnaire; PHQ-9) [30], anxiety (Generalized Anxiety Disorder Assessment; GAD-7) [35], sleep self-efficacy (Sleep Efficacy Scale; SES) [36], and motivation to change sleep behavior will also be assessed Table 1. These assessments except for motivation to change sleep behavior will be done at baseline, following the intervention, and 1-year later. Motivation to change sleep behavior will only be completed at baseline.

4.7. Polysomnography (PSG)

The PSG will be conducted at the clinical sleep lab. The PSG will be used for screening purposes and baseline assessment of slow wave sleep. PSGwill be completed again following the intervention and 1-year later. Participants will be prepared for PSG sleep monitoring using standardized techniques [38] including six electroencelphalogram (EEG) sensors to measure brain wave activity placed according to the international system for electrode placement [39], two eye sensors to record horizontal eye movement (electro-oculogram, EOG), five electromyogram (EMG) sensors (three placed on chin; two on the less-affected lower extremity) to assess muscle activity. Physiological signals will be recorded using Nihon Kohden equipment (Foothill Ranch, CA) which is recognized for superior EEG data collection. Other instruments include a nasal airflow sensor, comfortable belts around the thorax and abdomen to monitor respiratory effort, a finger probe to assess pulse oximetry, and a microphone to monitor snoring. Each study session is digitally video recorded. The sleep parameters of interest that will be calculated include: total sleep time, sleep period time, and % sleep period time spent in stage N1, N2, N3 (also called slow wave sleep) and REM sleep. The sleep records will be scored according to standardized scoring criteria [38].

4.8. Blood draw

A blood draw will take place during a separate visit. A trained phlebotomist will draw blood (20 ml) into Acid Citrate Dextrose Vacutainer tubes for genomic DNA extraction. APOE genotyping will be completed using restriction enzyme isotoping. APOE4 genotype will be used in secondary analysis.

4.9. MRI and PET imaging

Fifty participants will be enrolled in a substudy to examine the efficacy of CBT-I on reducing the rate of Aβ deposition in older adults with symptoms of insomnia (exploratory aim). Florbetapir PET images will be obtained on a GE 64 slice PET/CT MIDR scanner. The scanner is accredited by the American College of Radiology (ACR) and our physicists perform annual required testing by scanning an Esser PET phantom with 18F to assess SUV range, contrast resolution, spatial resolution, and uniformity. In addition to the ACR annual testing, the nuclear medicine department routinely performs quality control procedures on a daily, weekly, and quarterly basis. Participants 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 min). Participants will receive a single IV bolus of Florbetapir (370 MBq) followed by 2 brain PET frames of 5 min duration acquired continuously, approximately 45 min post-dose injection. Frames are reconstructed to a single attenuation corrected PET image in native space.

Amyloid burden will be quantified using a method developed in consultation with Avid and consistent with recent ADNI protocol [40]. This method maximizes longitudinal spatial stability by co-registering baseline and follow-up PET images using SPM8. PET scans are then co-registered with corresponding baseline MRI. Mean Florbetapir signal will be extracted from predefined frontal, anterior cingulate, posterior cingulate, parietal, and temporal ROIs using an aggregate of subregions.

5. Intervention

Participants will be randomized into either a group that received CBT-I or an active control group.

5.1. Cognitive behavioral therapy for insomnia (CBT-I)

The CBT-I program is a 6-week in-person one-one-one program with a research personal who is trained in providing CBT-I. A standardized CBT-I program will be used [41]. Participants will maintain a sleep diary during the course of the program to aid in tailoring the program, discussion of adherence, and to determine modification of time in bed restriction at each visit. Also, goals are set at each session and evaluated at the subsequent session. Videos and handouts will be used to augment verbal instruction and facilitate retention. The general sessions outlines are as follows with each session lasting 45-60 min:

Session 1: Discuss overall goals of the study. Educate the participant about the physiological methods of sleep using the two processes of sleep model [42] and the course of insomnia using the 3P model of insomnia [43]. Collaboratively set time in bed restriction and discuss strategies for stimulus control. Discuss sleep hygiene education.
Session 2: Review sleep hygiene. Introduce diaphragmatic breathing and deep breathing as relaxation technique to reduce arousal.
Session 3: Introduce mindfulness as a technique to reduce arousal. Cognitive therapy for negative sleep beliefs if indicated.
Session 4: Follow-up regarding negative sleep beliefs. Introduce progressive muscle relaxation as relaxation technique to reduce arousal.
Session 5: Reinforce and/or continue to tailor various techniques.
Session 6: Assess global treatment gains, discuss relapse prevention and maintenance of sleep gains.

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

5.2. Active control

Participants randomized into the Active Control (AC) group will attend 6 weekly 45–60 min sessions that include stretching and thinking activities (i.e., playing board games, puzzle games, or Nintendo Wii) with a graduate research assistant to control for socialization and contact with research personnel.

6. Same size and statistical analysis plan

6.1. 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 a two-sample t-test approach, but we anticipate even greater precision as we propose 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 Aβ measures, which will allow for effect estimation within approximately 0.65 standard deviations in magnitude based on 95% confidence interval calculations.

6.2. 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.

6.3. 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 Aβ measures, we will use linear regression to predict change in Aβ 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.

6.4. Exploratory aim

We hypothesize 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 follow-up 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 Aβ 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 considering 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.

7. Discussion

This randomized control trial will be the first study to examine the efficacy of a behavior sleep intervention on improving cognitive function and reducing the rate of Aβ deposition in older adults with symptoms of insomnia. Despite the strong links between sleep disruptions, cognitive decline, and risk of developing AD, no study to date has examined if sleep enhancement as a lifestyle intervention to prevent AD.

People with insomnia have increased risk of reduced cognitive function [4,44] and structural brain changes [19]. Furthermore, poor sleep quality [6,45] and reduced SWS [46] has been associated with increased Aβ deposition in cognitively normal adults. Up to 40% of older adults experience chronic insomnia [2], and chronic insomnia has been shown to increase the risk of developing AD [3]. Furthermore, approximately 15% of AD may be prevented by an efficacious intervention aimed to reduce sleep disturbances and sleep disorders [1]. 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 [9,11] and is more effective long-term than pharmacological interventions [26].

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.

7.1. Anticipated challenges and limitations

Because enrollment in this study is for 1 year, we anticipate adherence to the principles learned from the CBT-I intervention and retention in the study may be a challenge. We will work to encourage participants and identify problems that may be barriers to adherence and retention if needed. We anticipate the monthly phone calls with participants in the CBT-I group will help facilitate maintenance of sleep gains, adherence to the principles learned from the intervention, and retention in the program. We are also over-enrolling to allow for <20% attrition. Recruitment for clinical trials is often a challenge. However, we will address this challenge by utilizing multiple recruitment sources as previously described.

8. Conclusion

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 [47]. This proposed study is innovative because no prior studies have targeted sleep disturbances as a possible opportunity to impact the development of AD.

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Author contribution

Catherine Siengsukon: owner and CEO of Sleep Health Education LLC, Michelle Drerup: consultant for Go! To Sleep CBTi program, Jared Bruce: Funding from Genzyme, MS Society, Med IQ, National Hockey League.

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