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RESEARCH ARTICLE

Ketogenic dietary lifestyle intervention effects on sleep, cognition, and behavior in mild cognitive impairment: Study design

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Abstract

Introduction: Sleep and diet are modifiable risk factors for Alzheimer's disease (AD) that may be salient areas for the development of preventive intervention strategies against dementia in people with mild cognitive impairment (MCI). Sleep disturbances account for up to 15% of the population attributable risk for AD. Diet influences sleep quality, such that diets high in sugars, fat, and processed food affect sleep quality and cognition in older adults. The combination of poor sleep and diet health may increase risk for dementia in people with MCI, yet it is unknown how intervening on diet may influence sleep health.

Methods: The MCI Sleep Study assesses longitudinal changes in objective and subjective measures of sleep between two investigational diet groups in the Brain Energy for Amyloid Transformation in Alzheimer's Disease study: the modified Mediterranean ketogenic diet (MMKD) and the American Heart Association diet. Objective sleep assessments include an in-home sleep study using the WatchPAT Central Plus (Itamar Medical, Ltd) at baseline and the end of the 4-month diet intervention. Subjective sleep questionnaires include the Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index. The MCI Sleep Study outcome measures include longitudinal change in cognitive performance, mood, behavior, and quality of life.

Results: Study recruitment is currently ongoing. We hypothesize the low-carb MMKD diet to have a beneficial impact on sleep health in individuals with MCI. Pre- and post-diet changes in sleep metrics across diet groups will be examined using mixed effects analysis of variance models.

Discussion: Early assessment of chronic sleep and diet behaviors may be vital in understanding when interventions are necessary and the lifestyle modifications that should accompany future AD prevention and therapy recommendations.

KEYWORDS
diet intervention, mild cognitive impairment, prevention, sleep

1 | BACKGROUND

Sleep and diet are modifiable risk factors for Alzheimer's disease (AD)[1] that may be salient areas for the development of preventive intervention strategies against dementia. Sleep influences brain structure and function; however, many older adults do not get the recommended 7 to 8 hours of nightly consolidated sleep. Sleep disturbances account for up to 15% of the population attributable risk for AD[2] and are associated with greater amyloid deposition on positron emission tomography (PET) scan and lower cerebrospinal fluid (CSF) amyloid beta ($A\beta_{42}$) concentration.[3,4] Diet quality has also been linked to AD with slower progression to dementia associated with higher adherence to healthy Mediterranean dietary patterns.[5,6] In people with mild cognitive impairment (MCI), non-pharmacological interventions involving diet and sleep provide opportunities to assess and modify risk before the onset of AD.

Diet influences sleep quality, such that diets high in sugars (glucose), fat, and processed food affect sleep quality, and cognition in older adults.[7–9] A key feature in the pathological course of AD is the diminished ability of the brain to use glucose. This reduction in the uptake of glucose can be measured via PET scanning and can be seen many years, even decades, before clinical symptoms.[10] In light of these findings, ketones, an energy source made by the liver in the absence of glucose, may provide a more efficient fuel for cellular respiration in neurons with less cellular waste by-products compared to glucose.[11,12] This may serve as a potential therapeutic target for changes in brain glucose and insulin associated with the development of AD.

In general, a ketogenic diet (KD) is a very low carbohydrate diet from which ketones rather than glucose are the primary energy source for cells. The KD is a proven treatment for epilepsy, reducing seizures dramatically.[13,14] One explanation for the powerful effects of the KD for seizure control is reduced neuronal hyper-excitability, a state of neuronal dysfunction also present in early stages of MCI and AD.[15] Mechanisms underlying the effectiveness of the KD are not definitively known, but candidates include reduction of neuronal hyper-excitability through glutamatergic inhibition due to increased production of γ-aminobutyric acid (GABA), and KD enhancement of mitochondrial metabolism with corresponding activation of adenosine triphosphate–sensitive K+ channels.[16] Ketones modulate glutamate metabolism, increasing availability of the inhibitory neurotransmitter GABA and may thus restore inhibitory–excitatory balance within the central nervous system (CNS).[17] Supporting this possibility, CSF GABA levels increased after a 4-month KD intervention in epileptic patients, and greater GABA increase was associated with better seizure control.[18] In addition, these neuronal changes may impact the production and interstitial fluid clearance of $A\beta_{1\text{-}42}$.[19] The KD also improves sleep in epilepsy patients, demonstrated by increased percentage of rapid eye movement (REM) stage sleep after 3 months.[20] It is possible that the KD may improve sleep disturbances in other populations as well, such as MCI. In MCI, reduced time in REM stage sleep is associated with progression to AD.[21] One study showed that with each 1% decrease in time spent in REM sleep, there is an associated 9% increase in risk for all-cause dementia.[22] The association of REM sleep and cognitive decline may be linked to reduced memory consolidation that occurs during this stage of sleep.[23]

Chronic sleep disturbances characterized by sleep disordered breathing (SDB) can also have adverse effects on cognitive function and increase risk of cognitive decline and impairment—including MCI and AD.[24,25] Potential mechanisms to support an association between SDB and cognitive impairment include chronic hypoxemic effects on inflammation,[26] glucose regulation,[27] metabolic syndrome,[27] and brain white matter damage,[28] which are all well-established risks for cognitive decline and AD. Chronic exposure to sleep disturbances may also contribute to or ignite neuropathological processes associated with AD. Chronic intermittent hypoxia (IH), a hallmark feature of SDB, leads to significant neuronal atrophy and degeneration prior to cognitive symptoms, and may therefore play a crucial role in the progression to AD.[29] In animal models, brain $A\beta_{42}$ and phosphorylated tau protein, the pathological hallmarks of AD, increase with IH,[30] and sleep deprivation.[31]

Two major benefits of quality sleep include optimal cognitive performance and improved mood. Sleep disturbances are a common neuropsychiatric symptom in adults with MCI.[32] Previous work has shown nighttime sleep/behavior disturbance, measured using the neuropsychiatric inventory questionnaire (NPI-Q), occur in >40% of participants with MCI.[32,33] Further, individuals with MCI who have obstructive sleep apnea have significantly higher nighttime sleep disturbances, apathy, appetite changes, delusions, and hallucinations measured on the NPI-Q, compared to those without sleep apnea.[33] Lifestyle intervention studies traditionally have not included sleep as a primary outcome measure, despite findings that lifestyle changes, most typically diet and exercise, increase the sleep drive, alter sleep architecture, and reduce the burden of obstructive sleep apnea.[25,34,35] While the ability to achieve optimum sleep quality can become more difficult with age, and even more so in neurodegenerative disorders, controlled clinical trials are needed to effectively test whether intervention on lifestyle factors impacts the course of sleep disturbances and subsequent disease progression. Thus, this article describes the study design for our MCI Sleep Study measured in connection to a longitudinal diet intervention.

The MCI Sleep Study is an ancillary study to the Brain Energy for Amyloid Transformation in Alzheimer's Disease (BEAT-AD) study, a 4-month phase II randomized controlled trial (ClinicalTrials.gov: NCT03472664). The intervention includes two experimental diets, a modified Mediterranean ketogenic diet (MMKD) compared to a low-fat American Heart Association Diet (AHAD). The MCI Sleep Study assesses whether the diet treatments alter key sleep characteristics such as total sleep time, time spent in sleep stages, and sleep hypoxia measures, and improves episodic memory, executive function, neuropsychiatric symptom burden, and quality of life. Sleep changes will be assessed within MMKD and AHAD groups and between groups for sleep, cognitive performance, and neuropsychiatric symptoms. In addition, the MCI Sleep Study will assess the potential role of baseline SDB as a moderator of diet response using home-based sleep technology. Thus, the MCI Sleep Study is designed to provide measures that optimally capture diet-induced changes in sleep health.

2 | METHODS

2.1 | Study design and overview

The MCI Sleep Study assesses longitudinal changes in objective and subjective measures of sleep between two investigational diet groups, the MMKD and the low-fat AHAD. The experimental MMKD[36] reduces carbohydrates, which is needed for ketosis, and includes the powerful benefits of Mediterranean diet components that are associated with healthy cognitive aging.[37] The AHAD is a regimen to reduce cardiovascular disease and has been used as a control in previous studies.[35] The primary objective of the BEAT-AD study is to assess the safety and feasibility of a 4-month MMKD compared to the control AHAD in adults with amnestic MCI (aMCI), and determine its effects on a key AD biomarker of disease severity, the CSF A$\beta_{42/40}$ ratio.

Objective sleep assessments include an in-home sleep study using the WatchPAT Central Plus (Itamar Medical, Ltd) at baseline and end of the diet intervention. Subjective sleep questionnaires (described below) are administered during cognitive assessments at baseline, mid-intervention, and the end of the intervention. The MCI Sleep Study outcome measures include cognitive performance, mood, and behavior as well as quality of life assessment. The primary hypothesis is that the MMKD will increase cognitive performance, quality of life ratings, and the time spent in REM and deep sleep stages, while reducing sleep disruptions and neuropsychiatric symptom burden.

The BEAT-AD study procedures include eligibility screening and cognitive testing to determine aMCI. Participants are then enrolled and complete baseline procedures including amyloid PET scan to determine brain amyloid burden status. Amyloid PET status is used in follow-up responder analyses; both amyloid positive and negative participants are enrolled. Outcome measures are collected at baseline and at the end of the diet intervention period, and include CSF AD biomarkers (Aβ_{42}, total Aβ_{40}, tau, phosphorylated tau) and magnetic resonance imaging (MRI; T1/T2 fluid-attenuated inversion recovery [FLAIR], pseudo-continuous arterial spin labeling [pcASL], neurite orientation and dispersion density imaging, susceptibility weighted imaging, and resting state functional MRI).

2.2 | Ethical conduct of study

The Wake Forest University School of Medicine Institutional Review Board approved the BEAT-AD study protocol. All participants enrolled in the BEAT-AD study sign an informed consent document and all also complete the MCI Sleep Study procedures.

2.3 | Participants and inclusion criteria

Participants aged 55 to 85 years are recruited from the Wake Forest Alzheimer's Disease Research Center and the surrounding community. Participants are required to meet National Institute on Aging–Alzheimer's Association criteria for aMCI.[38] This includes a complete cognitive and behavioral test battery with adjudication by an expert consensus panel. Participants' medical condition and medications must be stable prior to baseline assessments. Target enrollment is 120 participants, with equal numbers of men and women. Every effort is made to enroll an ethnically diverse sample that is representative of the geographical region. Full inclusion and exclusion criteria for the BEAT-AD and MCI Sleep Study are provided in Table 1.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed relevant literature with PubMed using search terms related to sleep health, home-based technology in the elderly, cognition, diet interventions, and the relationship of these factors with mild cognitive impairment (MCI) and Alzheimer's disease.
2. **Interpretation**: The MCI Sleep Study assesses longitudinal changes in objective and subjective measures of sleep between two investigational diet groups, the modified Mediterranean ketogenic diet and the American Heart Association diet. We use home-based sleep technology pre and post the 4-month diet intervention.
3. **Future Directions**: At the completion of this ongoing clinical trial, future work will analyze the association of objective and subjective measures of sleep hypoxia, disruptions, time spent in sleep stages, sleep quality, and sleepiness with longitudinal changes in cognition, mood, behavior, and quality of life.

2.4 | Sleep study measures

2.4.1 | Objective sleep measures

The WatchPAT Central Plus (WP) is used to obtain objective measures of sleep pre- and post-diet intervention. The WP is a US Food and Drug Administration–approved device for home-based sleep studies. The WP is designed to quantify oxygen desaturations, apneas, hypopneas, sleep staging, peripheral arterial tone pulse, body movement, and even snoring decibel. The WP has high sensitivity, specificity, and validity compared to polysomnography (PSG), the gold standard for sleep assessment.[39] The WP measures changes in peripheral arterial tone (PAT) and oxygen desaturations using a finger probe.[39,40] Respiratory movement is measured from the chest sensor, which also allows for the differentiation of central versus obstructive apneic events. In addition, the WP wrist-worn actigraph identifies sleep stages and body position. The combination of these major components are used to derive the multiple sleep metrics of the WP device via a proprietary algorithm.[41–43] Sleep data from the WP is processed and checked for quality of signal after each home-based sleep study in the Itamar

TABLE 1 Participant inclusion and exclusion criteria

Inclusion criteria
1. Male or post-menopausal female
2. Age 55 to 85 years inclusive
3. Diagnosis of amnestic MCI (single or multi-domain)
4. A study partner able to provide collateral information on the participant
5. Stable medical condition
6. Stable on medications
7. Able to complete baseline assessments
Exclusion criteria
1. Diagnosis of neurodegenerative illness (except for MCI)
2. History of a clinically significant stroke;
3. Current or history in past year of focal brain lesion, head injury with loss of consciousness, or DSM-IV criteria for any major psychiatric disorder
4. Sensory impairment (i.e., visual or auditory) precluding study participation
5. Diabetes that requires current use of diabetes medications
6. Clinically significant elevations in liver function tests
7. Active neoplastic disease (stable prostate cancer and non-melanoma skin cancer is permissible)
8. History of epilepsy or seizure within past year
9. Contraindications for MRI (claustrophobia, craniofacial metal implants, pacemakers)
10. Significant medical illness or organ failure, such as uncontrolled hypertension or cardiovascular disease, chronic obstructive pulmonary disease, liver disease, or kidney disease
11. Use of the following medications: anticonvulsants, drugs with potential interfering central nervous system effects (other than cholinesterase inhibitors or memantine), medications with significant anticholinergic activity, anti-parkinsonian medications, or regular use of narcotic analgesics
12. If female, menstruation in the past 12 months
13. Major digestive disorders, absorption issues, or surgeries that may be exacerbated by diet changes
14. Untreated hypothyroidism or B12 deficiency
15. Use of resveratrol, coenzyme Q10, coconut oil/other medium chain triglyceride-containing supplements above 2000 mg

Notes: Inclusion and exclusion criteria for the BEAT-AD and MCI Sleep Study. Study inclusion is based upon compliant participation in the study diet and medical eligibility for all study procedures.
Abbreviations: BEAT-AD, Brain Energy for Amyloid Transformation in Alzheimer's Disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

Medical zzzPAT software. A trained reviewer will make manual adjustments to ensure sleep data accuracy. MCI participants are provided with instructions and a demonstration on how to use the device in the clinic. Initiating the sleep study requires a single push of the power button by the participant, or their study partner, to begin the overnight test. The comprehensive array of sleep measures will be used to assess sleep quantity, efficiency, and continuity throughout the night. The complete list of sleep metrics derived from the nine output channels are provided in Table 2.

2.4.2 | Sleep diary

Sleep diaries are distributed with each WP device. The sleep diary includes questions such as the date of the sleep test, time in and out of bed, as well as a description of last food and drink items consumed prior to using the WP. The morning after completing the WP test, participants provide feedback on their ability to use the device and indicate whether their night sleep was typical. In addition, participants indicate whether they have a history of sleep apnea requiring the use of a continuous positive airway pressure (C-PAP) machine or oxygen; use sleep medications; or consumed alcohol, caffeine, or tobacco within 4 hours of the sleep test. Participants also provide their report of the time they fell asleep, the number of times they awoke or laid awake, and the number of times they got out of bed.

2.4.3 | Subjective sleep measures

Sleep questionnaires were administered to participants at four time points throughout the study and during the follow-up period. These questionnaires assess sleep quality measured by the Pittsburgh Sleep Quality Index[44] and excessive daytime sleepiness measured by the Epworth Sleepiness Scale.[45]

2.4.4 | Neuropsychiatric symptoms and quality of life

Neuropsychiatric symptoms and depression are assessed using the NPI-Q[46] and the Geriatric Depression Scale—short form.[47] Daily behaviors and quality of life are measured using the Functional Activity Questionnaire (FAQ)[48] and the Quality of Life Assessment in Alzheimer's Disease (QoL-AD).[49]

2.5 | BEAT-AD diet intervention

Enrolled participants with aMCI are randomized on a 1:1 basis to either the MMKD or AHAD study diets based on baseline age, sex, and Mini-Mental State Examination (MMSE) score. The MMKD, a very low carbohydrate diet of <20 grams/day aimed at inducing ketosis, is the experimental diet. The AHAD is a low-fat diet, typically ≤40 grams/day and no more than 30% of calories derived from fat, serves as the control diet. The amount of carbohydrate (and fat) is the main variable manipulated between the two diets over the 4 months or 16 consecutive weeks period. The typical macronutrient composition (expressed as % of total calories) is provided in Table 3.

Participants randomized to the MMKD arm are asked to keep their daily carbohydrate consumption around 5 g of carbs per meal

TABLE 2 The WatchPAT 200 Central Plus channel outputs and automated sleep variables derived from the zzzPAT scoring software

Data File	Channel output	Description
	WP stages	WatchPAT algorithm derived sleep stages; light sleep, REM, deep sleep, wake
	PAT	Peripheral arterial tone measured via pulse in finger sensor
	PAT amplitude	Graphed PAT amplitude throughout the sleep period
	Pulse rate (bpm)	Pulse rate measured by beats per minute from the finger sensor
	SaO2 (%)	Whole night oxygen saturation percentage measured in 1 s increments
	Respiratory movement	Respiration measured via chest sensor in one second increments
	Actigraph	Activity counts measured via the wrist worn actigraph in 1 s increments
	Snore (dB)	Snoring decibel >40 hz measured via the chest sensor microphone
	Body position	Body position of prone, right, left, supine measured via wrist worn WatchPAT
Sleep Report	**Sleep variable**	**Description**
	Total sleep time	Derived from the total time spent asleep while in bed
	Sleep maintenance efficiency	Percentage of time in bed (or total recording time) spent asleep
	REM-stage sleep %	Percentage of sleep time spent in REM-stage sleep
	Deep-stage sleep %	Percentage of sleep time spent in in deep sleep stage
	Light-stage sleep %	Percentage of sleep time spent in a light sleep stage
	AHI score	Apneas and hypopneas per hour average across sleep period
	RDI score	Respiratory disturbances per hour average across sleep period
	ODI score	Oxygen desaturations per hour average across sleep period
	Sleep latency (min)	Time between the beginning of the recording and initiation of sleep period
	REM sleep latency (min)	Time between the beginning of sleep period and the initiation of REM sleep
	Number of wakes	Total number of awakenings during sleep period

Note: The WatchPAT (WP) 200 Central Plus (Itamar Medical, Ltd) channel outputs and sleep report variables generated by the zzzPAT software.
Abbreviations: AHI, apnea hypopnea index; dB, decibel; ODI, oxygen desaturation index; PAT, peripheral arterial tone; RDI, Respiratory disturbance index REM, rapid eye movement; SaO2, oxygen saturation,

TABLE 3 The modified Mediterranean ketogenic and American Heart Association diets macronutrient percent composition

Macronutrient	MMKD	AHAD
Carbohydrates	5%–10%	35%–40%
Fat	60%–65%	25%–30%
Protein	30%	30%

Note: The macronutrient composition, expressed as the percentage of total calories for the modified Mediterranean ketogenic diet (MMKD) and the American Heart Association diet (AHAD). The study total daily calories are isocaloric to pre-diet caloric intake determined by baseline resting metabolic rate testing for each participant.

throughout the 4-month intervention and the amount of fat and protein may be variable. Higher fat foods (preferably low in saturated fats) are added liberally to the diet plan. Throughout the study, participants on the MMKD are encouraged to avoid low-carbohydrate store-brought products and artificially sweetened beverages. The MMKD group are also encouraged to eat plentiful fish, lean meats, and nutrient-rich foods. Participants on the AHAD are encouraged to limit the amount of fat intake to <30% of total calories per day, while eating plentiful fruits, vegetables, and carbohydrates. Participants are encouraged to consume the same number of calories per day as they did in their pre-study diet.

Participants on both diets receive the same daily multivitamin supplement (Centrum Silver), and are provided with a food scale for use while in the study. Those randomized to the MMKD also receive a supply of olive oil while consuming the study diet. Participants are asked to discontinue supplements for the duration of the study including resveratrol, CoQ10 (coenzyme Q10), coconut oil/other medium chain triglyceride containing supplements (i.e., Axona), or curcumin, as they may influence bioenergetic status and may interfere with the interpretation of study results.

2.5.1 | Diet implementation and compliance

The BEAT-AD study registered dietitian develops daily meal plans for each study participant based upon their food preferences and caloric needs as determined by resting metabolic rate assessment, pre-study food records, and activity levels. Participants have weekly in-person visits for the first 2 months during which their daily food diary is reviewed and compliance rated, followed by bi-monthly in-person visits, with phone calls on the off weeks. Capillary ketone and glucose

TABLE 4 The BEAT-AD diet intervention study primary, secondary, and exploratory outcome measures

	Procedure	Outcome measure
Primary outcome	Lumbar puncture	CSF $A\beta_{42/40}$ ratio
Secondary / exploratory outcomes	Lumbar puncture	CSF total tau, phosphorylated tau 181, ceramides, fatty acids, redox proteomic profile
	PET-CT	Global ^{11}C-acetoacetate uptake Global ^{18}F-fluorodeoxyglucose uptake P-Alzheimer's disease (ALZ/PMOD)
	MRI	Hippocampal volume AD signature cortical thickness Default mode network connectivity PCASL posterior cingulate perfusion
	Blood	Mitochondrial basal, maximal, spare respiratory capacity OXPHOS transcriptomic index OXPHOS methylation index Exosome insulin resistance index
	Cognition/function	Preclinical Alzheimer Cognitive Composite (Primary) ADAS-Cog 12 Executive function tests Activities of daily living-mild cognitive impairment

Notes: Study outcomes for the diet intervention study included the primary outcome of change in CSF levels of $A\beta_{42}$. Secondary and exploratory outcomes include a range of cellular, molecular, plasma, cognitive, and functional changes across key study procedures of lumbar puncture, PET, MRI blood sample collection, as well as cognitive and functional assessments.

Abbreviations: $A\beta$, amyloid beta; AD, Alzheimer's disease; ADAS-Cog 12, Alzheimer's Disease Assessment Scale–Cognitive subscale; BEAT-AD, Brain Energy for Amyloid Transformation in Alzheimer's Disease; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; OXPHOS, oxidative phosphorylation; PET, positron emission technology.

levels are measured in person weekly for the first 2 months, then monthly.

Participants are required to supply the majority of their own food based upon a daily meal plan, food list, and other educational materials provided. In the first 4 weeks of the study, participants receive five meals per week prepared and packaged by the Metabolic Kitchen of the Atrium Health Wake Forest Baptist Clinic Research Unit. These meals are designed to match the nutrient guidelines of the randomly assigned study diet and assist participants in learning about appropriate ingredients for their meals. Participants are asked to keep their exercise levels stable throughout the study.

2.6 | Cognitive battery

Cognitive screening is completed using the Uniform Dataset (UDS) version 3.0 test battery. After screening and adjudication of cognitive status, eligible participants are enrolled in the study, and complete the cognitive battery at four time points throughout the study and follow-up period (pre-, mid-, post-, follow-up). The cognitive battery consists of the Preclinical Alzheimer Cognitive Composite (PACC),[50] category fluency, the Alzheimer's Disease Assessment Scale[51]—Cognitive subscale (ADAS-Cog) version 12, and the Geriatric Depression Scale (GDS). The study partner completes questionnaires related to the mood and daily activities of the participant at the pre-, post, and follow-up assessment visits; these include the Alzheimer's Disease Cooperative Study—Activities of Daily Living Scale (ADCS-ADL)[52] and FAQ. Participants also complete the MCI Sleep Study sleep questionnaires and NPI-Q at these visits.

2.7 | Other BEAT-AD study outcomes

BEAT-AD study participants complete additional study procedures throughout the 4-month diet period and 8-week follow-up. These include physical and neurological exam, vital measurements, blood draws, weekly finger stick, lumbar puncture, PET, magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DEXA) scanning, and stool sample collection. A complete list of primary, secondary, and exploratory measures is outlined in Table 4.

2.8 | Statistical analysis

Pre- and post-diet changes in sleep metrics across diet groups will be examined using mixed effects analysis of variance models. Baseline analyses include descriptive statistics of participants, summary sleep statistics for the aMCI sample and independent samples t-test comparison of sleep, cognitive and MRI measures between MMKD and AHAD groups. Inference will be based on a generalized linear model with the dependent variables consisting of change in % REM and change in % deep stage sleep from baseline to Month 4 (end of diet phase). General linear models will measure the interaction of sleep, diet, and cognition additively. These outcomes will be combined using a

multivariate analysis of covariance model with adjustment for sex, age, baseline MMSE score, body mass index, apolipoprotein E ε4 status, sleep medication use, baseline amyloid positivity, sleep apnea, insomnia, and C-PAP usage. In this model, all observed data could be included without special procedures for missing data, provided they are missing at random. The estimated differences will be combined using the ordinary least squares global test statistic by O'Brien[53] and discussed by Pocock et al.[54] Among the parent study enrollees, we anticipate $N = 120$ will provide valid baseline and 4-month sleep data. To date, study compliance in the wear and use of the WatchPAT is at 98%. The results of a power analysis using two-sided type 1 error of 0.05 and effect size of 0.5 indicated that 60 participants per group would provide 90% power.

3 | DISCUSSION

3.1 | Study overview

Currently, this trial is contributing valuable data on multiple objective sleep metrics in a large sample of individuals with aMCI. The baseline and longitudinal sleep data will provide insight into the relationship between sleep characteristics and cognition, and how intervening on diet influences these relationships. The MCI Sleep Study will investigate the effects of a MMKD on multiple dimensions of sleep health. This study uses a novel approach, home-based sleep technology in prodromal AD, to investigate modifiable risk factors for AD. Studies on objective measures of sleep have more recently set out to assess how sleep disruptions differentiate from normal age-related sleep changes. By leveraging the resources and data of the BEAT-AD study, we will be able to assess the relationships among diet composition, sleep, cognition, and behavior. Additionally, secondary and exploratory outcomes collected for the BEAT-AD study may be assessed in their association with our sleep metrics; these include: CSF Aβ42, Aβ40/, total tau and phosphorylated tau, brain cerebral perfusion, and amyloid PET positivity. Together these studies may construct a better understanding of the influence of lifestyle factors on MCI quality of life and cognitive decline and inform the development of a phase III intervention trial focused on diet as an intervention to slow progression of AD.

3.2 | Sleep studies in MCI

To date, one systematic review on sleep in MCI has quantified macro and micro sleep architecture changes compared to age-matched controls. Differences between individuals with aMCI versus normal cognition indicate lower slow wave sleep and sleep efficiency in aMCI.[55] Sleep metrics assessed via PSG or actigraphy between these two groups indicate no differences in total sleep time, sleep latency, REM percentage, or wake after sleep onset between these groups across 278 subjects in a meta-analysis of eight studies.[55] Differences along the AD continuum are important factors to assess, as less time in REM and deep sleep and greater sleep disruptions may reflect the progression to AD.[56,57] Our study will contribute to the limited data available on sleep characteristics and quality in people with MCI.

Our study is novel in that we will assess MCI sleep characteristics before and after a 4-month diet intervention. This will allow us to determine the impact of diet induced changes associated with the MMKD across multiple sleep metrics for individuals with MCI. Neuroimaging, CSF, and the recent advances in blood-based plasma biomarkers will provide invaluable data for secondary and exploratory analysis to assess the relationship of these measures with sleep health.

4 | SUMMARY

Overall, the MCI Sleep Study ancillary to BEAT-AD, a randomized controlled dietary intervention trial, will provide new knowledge regarding the impact of diet on sleep architecture sleep disruptions, cognition, and behavior in adults with MCI. Early assessment of chronic sleep and diet behaviors may be vital in understanding when interventions are necessary and the lifestyle modifications that should accompany future AD prevention and therapy recommendations.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest. Author disclosures are available in the supporting information.

REFERENCES

1. Edwards Iii GA, Gamez N, Escobedo G, Jr., Calderon O, Moreno-Gonzalez I. Modifiable risk factors for Alzheimer's Disease. *Front Aging Neurosci*. 2019;11:146.
2. Bubu OM, Brannick M, Mortimer J, et al. Sleep, Cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep*. 2017;40(1):zsw032.
3. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol*. 2013;70(12):1537-1543.
4. Liguori C, Mercuri NB, Izzi F, et al. Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's disease biomarkers changes. *Sleep*. 2017;40(5):zsx011.
5. Hill E, Goodwill AM, Gorelik A, Szoeke C. Diet and biomarkers of Alzheimer's disease: a systematic review and meta-analysis. *Neurobiol Aging*. 2019;76:45-52.
6. Wieckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. *Ageing Res Rev*. 2021;70:101397.
7. Hur S, Oh B, Kim H, Kwon O. Associations of diet quality and sleep quality with obesity. *Nutrients*. 2021;13(9):3181.
8. St-Onge MP, Mikic A, Pietrolungo CE. Effects of Diet on Sleep Quality. *Adv Nutr*. 2016;7(5):938-949.
9. Zuraikat FM, Wood RA, Barragan R, St-Onge MP. Sleep and diet: mounting evidence of a cyclical relationship. *Annu Rev Nutr*. 2021;41:309-332.

10. Mosconi L, Mistur R, Switalski R, et al. FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2009;36(5):811-822.
11. Croteau E, Castellano CA, Fortier M, et al. A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. *Exp Gerontol*. 2018;107:18-26.
12. Sokoloff L. Metabolism of ketone bodies by the brain. *Annu Rev Med*. 1973;24:271-280.
13. Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database Syst Rev*. 2016;2:CD001903.
14. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol*. 2008;7(6):500-506.
15. Stargardt A, Swaab DF, Bossers K. Storm before the quiet: neuronal hyperactivity and Abeta in the presymptomatic stages of Alzheimer's disease. *Neurobiol Aging*. 2015;36(1):1-11.
16. Milder J, Patel M. Modulation of oxidative stress and mitochondrial function by the ketogenic diet. *Epilepsy Res*. 2012;100(3):295-303.
17. Yudkoff M, Daikhin Y, Nissim I, et al. Response of brain amino acid metabolism to ketosis. *Neurochem Int*. 2005;47(1-2):119-128.
18. Dahlin M, Elfving A, Ungerstedt U, Amark P. The ketogenic diet influences the levels of excitatory and inhibitory amino acids in the CSF in children with refractory epilepsy. *Epilepsy Res*. 2005;64(3):115-125.
19. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373-377.
20. Hallbook T, Lundgren J, Rosen I. Ketogenic diet improves sleep quality in children with therapy-resistant epilepsy. *Epilepsia*. 2007;48(1):59-65.
21. Shinno H, Ishikawa I, Nobuo A, Yoshihito M, Horiguchi J, Nakamura Y. Alterations in rapid eye movement sleep parameters predict for subsequent progression from mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis Parkinsonism*. 2016;6(218):1000218.
22. Pase MP, Himali JJ, Grima NA, et al. Sleep architecture and the risk of incident dementia in the community. *Neurology*. 2017;89(12):1244-50.
23. Pace-Schott EF, Spencer RM. Sleep-dependent memory consolidation in healthy aging and mild cognitive impairment. *Curr Top Behav Neurosci*. 2015;25:307-330.
24. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. 2015;84(19):1964-1971.
25. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol*. 2014;13(10):1017-1028.
26. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med*. 2011;364(7):656-665.
27. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc*. 2008;5(2):207-217.
28. Chen HL, Lu CH, Lin HC, et al. White matter damage and systemic inflammation in obstructive sleep apnea. *Sleep*. 2015;38(3):361-370.
29. Daulatzai MA. Quintessential risk factors: their role in promoting cognitive dysfunction and Alzheimer's disease. *Neurochem Res*. 2012;37(12):2627-2658.
30. Fang H, Zhang LF, Meng FT, Du X, Zhou JN. Acute hypoxia promote the phosphorylation of tau via ERK pathway. *Neurosci Lett*. 2010;474(3):173-177.
31. Di Meco A, Joshi YB, Pratico D. Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles. *Neurobiol Aging*. 2014;35(8):1813-1820.
32. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry*. 2013;21(7):685-695.
33. Sanderlin AH, Todem D, Bozoki AC. Obesity and co-morbid conditions are associated with specific neuropsychiatric symptoms in mild cognitive impairment. *Front Aging Neurosci*. 2017;9:164.
34. Cao P, Cai Y, Zhang S, Wan Q. The effectiveness of different exercise modalities on sleep quality: a protocol for systematic review and network meta-analysis. *Medicine (Baltimore)*. 2020;99(29):e21169.
35. Daneshzad E, Mansordehghan M, Larijani B, et al. Diet quality indices are associated with sleep and mental health status among diabetic women: a cross-sectional study. *Eat Weight Disord*. 2022;27:1513-1521.
36. Neth BJ, Mintz A, Whitlow C, et al. Modified ketogenic diet is associated with improved cerebrospinal fluid biomarker profile, cerebral perfusion, and cerebral ketone body uptake in older adults at risk for Alzheimer's disease: a pilot study. *Neurobiol Aging*. 2020;86:54-63.
37. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol*. 2009;66(2):216-225.
38. Jack CR, Jr., Bennett DA, Blennow K, et al.NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
39. Hedner J, White DP, Malhotra A, et al. Sleep staging based on autonomic signals: a multi-center validation study. *J Clin Sleep Med*. 2011;7(3):301-306.
40. Choi JH, Kim EJ, Kim YS, et al. Validation study of portable device for the diagnosis of obstructive sleep apnea according to the new AASM scoring criteria: Watch-PAT 100. *Acta Otolaryngol*. 2010;130(7):838-843.
41. Zhang Z, Sowho M, Otvos T, et al. A comparison of automated and manual sleep staging and respiratory event recognition in a portable sleep diagnostic device with in-lab sleep study. *J Clin Sleep Med*. 2020;16(4):563-573.
42. Herscovici S, Pe'er A, Papyan S, Lavie P. Detecting REM sleep from the finger: an automatic REM sleep algorithm based on peripheral arterial tone (PAT) and actigraphy. *Physiol Meas*. 2007;28(2):129-140
43. Weimin L, Rongguang W, Dongyan H, Xiaoli L, Wei J, Shiming Y. Assessment of a portable monitoring device WatchPAT 200 in the diagnosis of obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2013;270(12):3099-3105.
44. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh sleep quality index. *J Psychosom Res*. 1998;45(1):5-13.
45. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545.
46. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239.
47. Javaid SI, Jerome YA. Geriatric depression scale: recent evidence and development of a shorter version. *Clinical Gerontologist*. 1986;5(1-2):165-173.
48. Pfeffer RI, Kurosaki TT, Harrah CH, Jr., Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37(3):323-329.
49. Korczyn AD, Davidson M. Quality of life in Alzheimer's disease. *Eur J Neurol*. 1999;6(4):487-489.
50. Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: The PACC5. *Alzheimers Dement (N Y)*. 2017;3(4):668-677.
51. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.
52. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's

Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11 Suppl 2:S33-S39.
53. O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics*. 1984;40(4):1079-1087.
54. Pocock SJ, Geller NL, Tsiatis AA. The analysis of multiple endpoints in clinical trials. *Biometrics*. 1987;43(3):487-498.
55. Cai S, Li T, Zhang L, et al. Characteristics of sleep structure assessed by objective measurements in patients with amnestic mild cognitive impairment: a meta-analysis. *Front Neurol*. 2020;11:577126.
56. Bliwise DL. Sleep in normal aging and dementia. *Sleep*. 1993;16(1):40-81.
57. Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer's disease. *Sleep Med Rev*. 2015;19:29-38.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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