NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Version Number	Version Date	Summary of Revisions Made
1.0	18 September 2018	Original version
2.0	12 December 2018	First Modification

NYU School of Medicine
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A SINGLE-CENTER, OBSERVATIONAL, LONGITUDINAL STUDY ON THE EFFECT OF SLOW WAVE SLEEP (SWS) CHARACTERISTICS AND RACE AND ETHNICITY ON AMYLOID BURDEN (A MARKER OF ALZHEIMER'S DISEASE RISK), AMONG COGNITIVELY NORMAL ELDERLY

Principal Investigator:	Ricardo Osorio, MD Department of Psychiatry NYU Center for Brain Health 145 E 32nd St. New York, NY 10016 (212) 263-3255
Additional Investigators:	Girardin Jean-Louis, PhD Department of Population Health NYU Center for Healthful Behavior Change 180 Madison, 7th floorNew York, NY 10016 (646) 501-2623
NYULMC Study Number:	*s18-01302*
Funding Sponsor:	NIH/NIA
ClinicalTrials.gov Number	*In preparation*

Initial version: 9.18.2018

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Drs. Osorio and Jean-Louis assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

%AF	African Ancestry
AA	African American
AC	Attenuation Correction
ADC	Alzheimer's Disease Center
AE	Adverse Event/Adverse Experience
AD_{PiB}mask	AD-vulnerable ROIs PiB SUVR values
AD	Alzheimer's Disease
Aβ	Amyloid Beta
AHI4%	Apnea Hypopnea Index with 4% desaturation
BEDTIME	Brain Sleep Deprivation MRI Effects
BMI	Body Mass Index
CAB	Community Advisory Board
CBI	Center for Biomedical Imaging
CBO	Community Based
CSF	Cerebrospinal Fluid
CVD	Cardiovascular disease
CVE	Cardiovascular events
CRF	Case Report Form
CBH	Center for Brain Health
CDR	Clinical Dementia Rating
CHBC	Center for Healthful Behavior Change
CNS	Central Nervous System
CT	Completion Time
DKI	Diffusion Kurtosis Imaging
EKG	Electrocardiogram
FU	follow-up
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated Inversion Recovery
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ISF	Interstitial Fluid
IRB	Institutional Review Board
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging

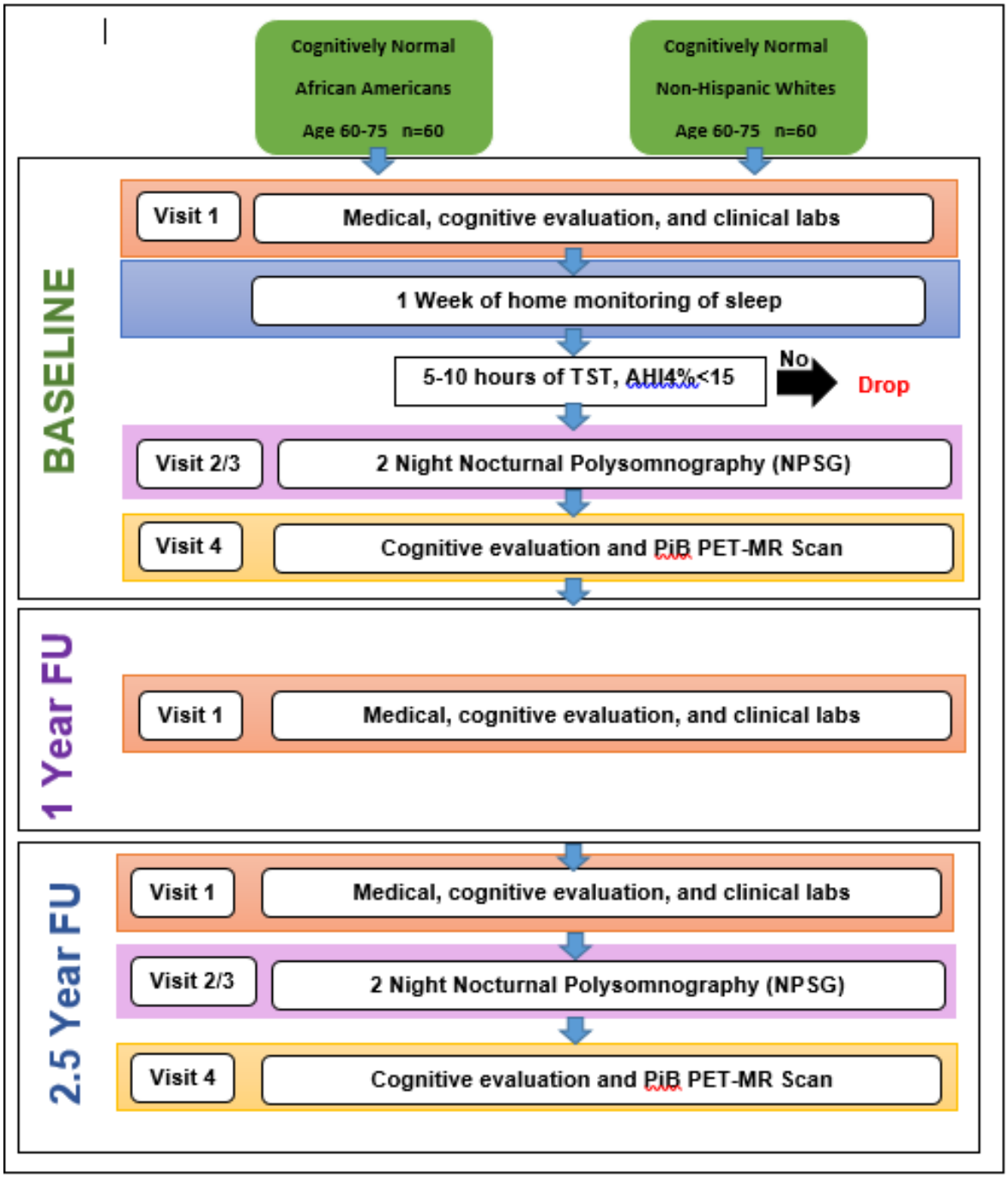
MCI	Mild Cognitive Impairment
mPFC	medial Prefrontal Cortex
n	Number
MSISC	Mount Sinai Integrative Sleep Center
NACC	National Alzheimer's Coordinating Center
NCRAD	National Cell Repository for Alzheimer’s Disease
NIH	National Institutes of Health
NIA	National Institute on Aging
NREM	Non-REM
NYULMC	NYU Langone Medical Center
NPSG	Nocturnal Polysomnography
OSA	Obstructive Sleep Apnea
PS	Plasma Serum
PET	Positron Emission Tomography
PCP	Primary Care Physician
PI	Principal Investigator
PHI	Protected Health Information
PiB	Pittsburgh Compound B
RDI	Respiratory Disturbance Index
SNR	Signal to Noise Ratio
SAE	Serious Adverse Event/Serious Adverse Experience
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
ROI	Region of Interest
SUVR	Standard Uptake Value Ratio
TST	Total Sleep Time
UTE	Ultrashort Echo Time
US	United States
UDS	Uniform Data Set
WASO	Wake After Sleep Onset
WHR	Waist to Hip Ratio
WML	White Matter Lesions

Protocol Summary

Title	**A SINGLE-CENTER, OBSERVATIONAL, LONGITUDINAL STUDY ON THE EFFECT OF SLOW WAVE SLEEP (SWS) CHARACTERISTICS, RACE AND ETHNICITY ON AMYLOID BURDEN (A MARKER OF ALZHEIMER'S DISEASE RISK), AMONG COGNITIVELY NORMAL ELDERLY**
Short Title	The **Sleep A**myloid, Slow **WA**ve **R**ace and **E**thnicity (Sleep AWARE) study
Brief Summary	African-Americans (AAs) have an increased prevalence of both Alzheimer's disease (AD) and vascular risk factors for AD such as diabetes and hypertension when compared to whites. However, in a recent community based study of non-demented elderly**, black race** was associated with higher amyloid burden after adjusting for vascular risk factors, suggesting the presence of additional physiological differences on AD-risk by race in the early stages of the disease. The purpose of this study is to test whether poor slow wave sleep (SWS) quantity (SWS duration) and quality (slow wave activity, SWA) is one of these physiological factors. To test these hypotheses, we will perform community outreach in barbershops, churches and senior centers in Brooklyn and other NYC boroughs with which we have created substantial ties in recent years. In consultation with community stakeholders, we will recruit 150 cognitively normal AA elderly (age 60-75) and 60 age, sex, BMI, income and education matched non-Hispanic whites from the same geographical areas. We will first perform a medical and cognitive evaluation (Visit 1). Participants will then undergo 2 nights of home sleep monitoring using an unattended device to exclude OSA, followed by 7 days of actigraphy with a sleep log to record sleep duration. Both devices will be returned by mail. Subjects with reported total sleep time (TST) between 5 and 10 hours and absence of moderate to severe OSA will be invited to perform a 2-night nocturnal polysomnography (NPSG) (Nights 1-2) and a PiB-PET MR scan (Visit 2).
Objectives	**Objective 1:** To test if African ancestry (%AF) is associated with short SWS duration and poor SWA in older AAs. **Objective 2:** To test the effect of race and its interaction with baseline short SWS duration/poor SWA on longitudinal amyloid deposition. **Objective 3:** To test the effect of race and baseline poor SWA on cognition. **Secondary Objective 2.1:** To test whether loss of sleep-dependent spatial navigational memory at baseline is a predictor of cognitive decline.
Methodology	30-36 month longitudinal study
Endpoint	Primary endpoint is longitudinal increase in amyloid deposition
Study Duration	5 years
Participant Duration	30-36 months

Population	210 cognitively normal elderly (Clinical Dementia Rating [CDR]=0), self-identified as African-American (AA) or non-Hispanic white (NHW), ages 60 to 75 years, with English as their primary language. The reason for only including native English speakers is due to the nature of the study and cognition being one of the outcomes of the study. The reason for including only African American blacks and NHW is the focus of this grant which is on African Americans and their African genetic ancestry and admixture. Based on our preliminary data an existing literature, in order for genetic admixture analyses to be applied rigorously, the control group needs to be of NHW. The definition of NHW are people in the United States who are considered racially white and are not of Hispanophone identity or the Hispanosphere (terms used to refer to Spanish-language speakers and the Spanish-speaking world as compared to for example English-speaking of French-speaking to name a few). Other non-English non-Hispanic white ethnicities will not be invited to participate due to the lack of adequate neuropsyschological tools and testers proficient in other native European languages and the confounding effects of immigration. These NHW participants will be located within the same zip codes as the AAs.
Study Sites	**NYU locations:** the Center for Brain Health (CBH) at NYULMC, the Center for Biomedical Imaging (CBI), NYU Langone Health, Department of Radiology, 660 1st Avenue **External Site:** the Mount Sinai Integrative Sleep Center (MSISC) (New York, NY)
Number of participants	210 participants expected to be enrolled with 150 cognitively normal African-American elderly and 60 non-Hispanic white.
Statistical Analysis	We will incorporate standard techniques such as omnibus tests and appropriate adjustments to significance (α) levels (*e.g.*, Bonferroni correction) for *post-hoc* contrasts to control for multiple comparisons. Both selection and attrition biases might occur. Appropriate techniques (*e.g.,* Heckman 2-stage approach (GEE Probit Model) and Monte Carlo (EM algorithm) will be used to address biases or missing data. Since only two time points will be analyzed, we will use linear regression models with the annual rate of amyloid change as dependent variable. Significance will be defined by $p<.05$ where p will be Bonferroni corrected when testing *post-hoc* contrasts.

Schematic of Study Design



1 Key Roles

Primary Site: NYU School of Medicine
Ricardo Osorio Suarez, M.D,
Assistant Professor
Department of Psychiatry (PI)
NYU School of Medicine
(212) 263-3255
Ricardo.Osorio@nyulangone.org

Girardin Jean-Louis, PhD,
Professor
Department of Population Health (PI)
Department of Psychiatry
NYU Center for Healthful Behavior Change
(646) 501-2623
Girardin.Jean-Louis@nyulangone.org

External Site: Mt. Sinai School of Medicine
Indu Ayappa, Ph.D,
Associate Professor
Department of Medicine (Sub-contract PI)
Icahn School of Medicine at Mount Sinai
(212) 241-1967
indu.ayappa@mssm.edu

David Rapoport, M.D,
Professor
Department of Medicine (Co-Investigator)
Icahn School of Medicine at Mount Sinai
(212) 481-1818
david.rapoport@mssm.edu

Andrew Varga, M.D and Ph.D,
Assistant Professor
Department of Medicine (Co-Investigator)
Icahn School of Medicine at Mount Sinai
(212) 241-6084
andrew.varga@mssm.edu

Collaborator: Columbia University Medical Center (Analysis of de-identified datasets only)
Giuseppe Tosto, MD, PhD
Assistant Professor
Department of Neurology
Columbia University Medical Center
Taub Institute for Research on Alzheimer's Disease and the Aging Brain
(212) 305-9274
Gt2260@columbia.edu

Danurys Sanchez
Senior Research Staff Associate
Columbia University Medical Center
Department of Neurology
G.H. Sergievsky Center and
The Taub Institute
(212)-342-3055

dls167@cumc.columbia.edu

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Sleep duration in America has gradually declined over the last four decades, with current average sleep duration being of approximately 6 hours[18]. Parallel to this decline, African Americans (AAs) have the

highest prevalence of long (≥9 h) and short sleep (≤6 h)[61-63], within the intervals commonly associated with morbidity and increased AD-risk[68-70]. AAs take longer to fall asleep[18-23], have lower sleep efficiency and have consistently shown to spend a smaller proportion of time in deep stages of non-REM (NREM) (also called slow wave sleep [SWS])[19;20;23-28;32]. Possible mediators underlying these racial differences in sleep include age, sex, obesity, psychosocial factors, health care behaviors and medical disorders[21;23;27;71-76]. A meta-analysis designed to estimate the magnitude of these variations in sleep, showed that racial/ethnic differences in sleep duration and continuity were moderated by the factors underlined above[23], while only psychosocial stressors (measured as perceived discrimination)[20;21;26] were partially associated with the decreases in SWS duration, suggesting that race still remained an important independent risk factor for decreased SWS among AAs. A recent study confirmed this finding showing that decreased SWS duration was associated with an increased percentage of African ancestry (%AF)[39] even after adjusting for several demographic, socioeconomic and clinical covariates. Further replication is warranted, but African ancestry has also been associated to increased risk for hypertension[77] and diabetes[78] both of which have been linked with reductions in time spent in SWS[79;80].

Approximately 20% of healthy adults have mild and 6.6% moderate-to-severe obstructive sleep apnea (OSA)[81], with a higher incidence occurring in the elderly[82]. AAs generally show a higher prevalence of OSA[33-36]. Specifically, in the Cleveland Family Study, AAs presented with OSA at a younger age[35], while Ancoli-Israel et al.[34] found that older AAs were 2.5 times more likely to have severe OSA. These findings are in agreement with another study of adults aged 40-60, where OSA rates were higher among minorities[33]. In contrast, both the Sleep Heart Health (7% AAs) and Scharf's et al. studies failed to show higher rates of OSA in AAs after controlling for obesity[83;84]. However, AAs from these studies suffered more excessive daytime sleepiness, in agreement to previous findings suggesting that OSA-associated symptoms might be more common in AAs[34;85]. Apnea occurs less commonly during SWS, as SWS is associated with a higher respiratory arousal threshold[86;87] and more stable breathing[88]. However, beyond a certain threshold of frequency, apnea in any sleep stage impairs entry into SWS. In addition, the temporal course of slow wave activity (SWA) has shown to be slower in mild OSA[89], and severe OSA patients show up to a 40% rebound in SWS duration during treatment with CPAP[90]. All the above findings suggest that changes in SWS are common in OSA patients. SWS disruption may therefore be another mechanism by which OSA increases AD risk[91-93].

In summary: certain ethnic groups are more likely to have disturbed sleep. AAs show clear independent differences in SWS characteristics but not in sleep duration or OSA prevalence when compared to whites, after controlling for socioeconomic factors, obesity or health care behaviors. These differences seem unrelated to other explanatory factors (expect for the partial effect of psychosocial stressors) and suggest that AAs may have less restorative sleep than whites. The brain consequences of these decreases in SWS are not known.

2.2 Rationale

Primary Aims. To examine: *i*) whether African Ancestry (%AF) is associated with decreased SWS duration and SWA; *ii*) the effects of race on longitudinal amyloid build-up and its interaction with baseline SWS duration and SWA in cognitively normal elderly; *iii*) the effects of race and its interaction with baseline SWA on longitudinal changes in global cognition, memory, executive function and a spatial navigational memory task. Exploratory aim. We will test whether loss of sleep-dependent spatial navigational memory at baseline is a predictor of cognitive decline at follow-up.

Rationale for ethnicity/nativity and clinical groups selection:

Multiethnic cohort studies provide better information about disease causation but they are expensive to design. We will focus on 150 African-American (AA) blacks since African or Caribbean-born are not equally admixed and inclusion of more ethnic groups would result in loss of power for Aim 1 and need for great increases in sample size. As a comparison group, we will include 60 matched non-Hispanic whites. Race will be represented both as binary (self-identified AA *vs*. self-identified white) and numeric (% of African ancestry). Irregular sleep-wake rhythms and extreme sleep durations may also increase AD risk[68-70]. The study will not formally test these sleep disorders, as these subjects are hard to recruit in community-based

studies (often reluctant to participate in studies that monitor sleep) and the focus is on SWS. Insomnia will be allowed as long as total sleep time (TST) is between 5-9 hours based on actigraphy recordings and sleep logs performed at home.

2.3 Potential Risks & Benefits

2.3.1 Known Potential Risks

The following risks and discomforts may be experienced during participation in the study. In spite of all precautions, medical complications may occur. These include not only physical injury, but also possible psychological, social or economic harm, discomfort or inconvenience, or breach of confidentiality. To minimize risks, all study personnel are highly trained and experienced; materials are kept in locked file cabinets and are only available to investigators and research personnel associated with the study. All materials sent to outside laboratories are anonymized and the codes are kept with the NYU CBH Contact-PI (Dr. Osorio, MD). Both NYU's CBH and the Center for Healthful Behavior Change (CHBC), which will be a collaborator on this study to help provide expertise in recruitment strategies, have excellent records of safekeeping patients' data and have never had a breach of security. In the event of an adverse event at NYU or MSISC there are medical personnel available.

1. Physical, Neurological and Psychiatric Exams:

For the standard clinical examinations, there are minimal to no risks associated with the testing. The main risk is a loss of privacy and every precaution is taken to ensure confidentiality. Other psychological risks include discovering a condition that was not previously known.

2. Psychometric Testing:

There are no risks associated with cognitive testing. Some individuals may experience fatigue or test performance anxiety. Periodic breaks will be available during cognitive testing.

3. Laboratory Analysis of Blood:

The potential risks of blood drawing may occasionally include pain, bruising, fainting, or a small infection at the puncture site. Sometimes a small amount of bleeding into the arm (hematoma) may occur.

4. Heart Tracing (EKG):

The back of the electrodes are adhesive and may be uncomfortable when they are removed. There are no other risks associated with an EKG other than discovering a heart condition that was not previously known.

5. Genotyping:

There are potential dangers in obtaining DNA information. Genetic testing can generate information about a subject's personal health risks and can cause or increase anxiety, damage family relationships, and/or compromise insurability, employability and lead to social discrimination. To greatly reduce the possibility of such psychological or social risks, genetic results will be coded and no personal identification will link the subject with the genotype. Genetic results will not be disclosed to participants. We will include recommended language about the certificate of confidentiality and its limitations to the consent form.

6. MRI Scan:

MRI scanning involves the use of powerful magnets delivering radio frequency energy. Therefore, patients who have implanted metal devices, such as pacemakers, certain aneurysm clips, or shrapnel or metal in the eye, skull or elsewhere in the body are at risk. There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radio frequency energy used in this study. Contrast agents are not used in this study. Some people feel claustrophobic in the MR or PET-MR scanners. The MR scanner produces loud tapping sounds during operation and earplugs are provided to all subjects. Other rare risks of MRI may include neuro-stimulation effects resulting in muscle twitches and tingling sensations, due to the rapid switching of magnetic fields, and a slight increase in body temperature that may occur in the presence and absorption of radio frequency energy. These are, however, very unlikely under current operational guidelines. In the very remote event that the magnet loses its magnetism, liquid

helium in the magnet will be released. The room is designed with ventilation systems to prevent accumulation of these gases.

7. ^{11}C-Pittsburgh compound-B (PiB) PET-MR scan:

There is the possibility of discomforts associated with venous catheters. These risks include: minor pain or soreness, lightheadedness and/or minor bruising at the site of the catheter insertions, and less commonly, the formation of a small clot or swelling of the vein and bleeding. A chance of infection also exists. Experienced medical personnel will be involved in venipuncture procedure to minimize the possible risks associated with the catheters. As the effective dose (ED) of PiB is about 2.93 mSv when the recommended activity of 412 MBq of PiB is administered, adverse reactions due to radiation are expected to occur with a very low probability. In addition, PET/MR eliminates the exposure to CT scans used for attenuation correction by the PET/CT systems, so the radiation included would be lower than that of a similar study using PET/CT. Critical organ gallbladder wall exposure is 23.03 mGy. PiB is an experimental substance and other individual responses are possible and cannot be predicted. The frequency of allergic reactions to PiB is not known.

8. Sleep Studies:

The in-laboratory NPSG sleep studies are identical to those performed in clinical practice and present almost no risks as we will be using the standard diagnostic protocol for all subjects presenting to the MSISC with sleep complaints meriting a sleep study. The sleep study has no risks beyond the minor irritation that attachment of the recording electrodes on the skin occasionally may cause.

D. ADEQUACY OF PROTECTION AGAINST RISKS:

1. Recruitment, Informed Consent and Incidental Findings:

This study will involve male and female African-American elderly and white volunteer subjects with a diagnosis of 'cognitively normal' (CDR=0). Informed consent is obtained from each subject using IRB approved consent forms. In the consent form and in discussion with an investigator, participants will be advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigators (Drs. Osorio and Jean-Louis). In the informed consent form (ICF), participants will be told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff and the possible exception of state or federal regulatory personnel. Several steps will be taken to minimize reactions of discomfort, embarrassment, fatigue, or boredom.

Interviews will be conducted by staff that are well trained and closely supervised by Ferdinand Zizi. The informed consent procedure explains the overall purpose of the study in straightforward terms, and explains the conditions of confidentiality. We encourage participants' questions and comments throughout the interview. For our questions about educational and cultural background, we emphasize that there is 'no right answer' to the questions. All participants are informed that they may refuse to answer any question and that they may discontinue the interview at any time without affecting their participation in the study or medical treatment. Participants are explicitly asked for their feedback, reactions, and strategies. Research staff that conduct follow-up interviews are blind to prior research diagnosis. All personnel of the study will have successfully completed the required education on protection of human research participants performed at NYU Langone Medical Center (NYULMC). In the ICF and in the discussion with members of the research team, participants will be advised that if the standard medical, neurological, or neuropsychological evaluation should uncover significant deficit or an emergent and previously undiagnosed medical condition, or if the blood assays reveal significantly abnormal findings, Dr. Butler will contact the participant to discuss the condition and, if permitted, contact the participant's physician or refer the participant to an appropriate medical professional for follow-up. A technician reviews each MRI scan as they are being acquired for major abnormalities. A licensed, board-certified radiologist will perform a safety review on every MRI scan and results will be communicated to study participants within 4 weeks of the date they are obtained. Findings of clinical significance, such as a mass, acute hemorrhage/infarct will trigger telephone notification of the subject by Dr. Tracy Butler, MD and will inform them that an abnormal result has been found, and instructing them to contact their primary care physician (PCP). In addition, with

permission, their PCP will be contacted and a report from the neuroradiologist will be sent to that physician. In the absence of clinically significant findings, the report of the neuroradiology review will be communicated to the participant in the form of a letter that describes the general findings; a more detailed radiological report is transmitted to the participant's PCP upon explicit request and retained in a permanent data base, but no direct telephone contact will be made. If the subject has no physician, and has a clinically significant finding, we will arrange for follow-up care at a local clinic.

2. Protection Against Risk:

a. PiB PET scans

PET-MR scanning involves the use of powerful magnets. Therefore, patients who have implanted metal devices, such as pacemakers, certain aneurysm clips, or shrapnel or metal in the eye, skull or elsewhere in the body are at risk. There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radio frequency energy used in this study. Contrast agents are not used in this study. Some people feel claustrophobic in the PET-MR scanners. The MR scanner produces loud tapping sounds during operation and earplugs are provided to all subjects. Other rare risks of MRI may include neuro-stimulation effects resulting in muscle twitches and tingling sensations, due to the rapid switching of magnetic fields, and a slight increase in body temperature. These are, however, very unlikely under current operational guidelines. In the very remote event that the magnet loses its magnetism, liquid helium in the magnet will be released. The room is designed with ventilation systems to prevent accumulation of these gases.

Amyloid Pittsburgh compound B (PiB) tracer:

There is no recommended dose for PiB. 300 MBq is the lowest dose that has been recommended in the human studies published thus far (Klunk WE, Ann Neurol. 2004 Mar;55(3):306-19; Scheinin NM J Nucl Med. 2007 Jan;48(1):128-33), but most studies published to date include doses from 370 to 555 MBq (for a Cochrane review see Zhang S, Cochrane Database of Systematic Reviews 2014, Issue 7), with 370 MBq being the lowest injected dose below which the scan 'should not be performed and be rescheduled' according to the PET Technical procedures ADNI methods published in May 10th 2007 Version 1.2

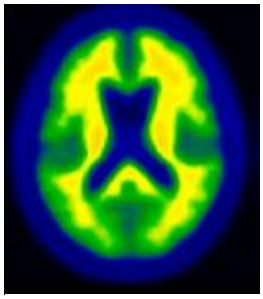


Figure 1. PiB PET Scan

(http://www.adniinfo.org/Scientists/doc/PET_PIB_Tech_Procedures_Manual_Suppl_v1.3.pdf) Given the: i) heterogeneity in injected doses; ii) the heterogeneity in the current conduct and interpretation of the tests; iii) the lack of defined thresholds for determination of test positivity; iv) the plan of sharing the scans from this study with both the ADNI LONI Image Data Archive (IDA) and NACC Imaging; and; v) in the low signal to noise ratio (SNR) with 412 MBq injections in the first scans performed at NYU we have decided to follow ADNI methods and inject 555 MBq of PiB to increase the quality of the signal and the external validity of our findings, as well as future use of the data by outside groups

b. Clinical Studies and Labs

There are minimal physical risks associated with the standard diagnostic procedures. Moreover, there are minimal psychological risks to patients who participate in this study.

c. Sleep Studies

The in-laboratory sleep studies are identical to those performed in clinical practice. The sleep study has no risks beyond the minor irritation that attachment of the recording electrodes on the skin occasionally may cause. There is the possibility that sleep might be disrupted by the fact that subjects will be sleeping in a new environment. All data will be coded and stripped of identifiers to protect the confidentiality of the subjects. All sleep analyses and in-labs will be performed within the MSISC (11 East 26th Street). MSISC has explicit emergency and procedure guidelines in place for dealing with medical emergencies that may arise.

2.3.2 Known Potential Benefits

Participants are made aware that the study does not provide clinical treatment and should not be used as a substitute for proper medical care with a physician; however, if the standard medical, neurological, or neuropsychological evaluation reveals significant deficit or an emergent and previously undiagnosed medical condition, or if the blood assays, or MRI scan reveal significant abnormalities, this information will be discussed with the participant and transmitted to their PCP. We do not expect the majority of participants to benefit directly from the research other than by financial remuneration for their time and effort. The potential benefits to society are considerable if this study reveals new information about new biological mechanism of AD risk in African-American elderly. Therefore, the risks to participants are reasonable in relation to the anticipated benefits to society.

3 Objectives and Purpose

3.1 Primary Objective

Aim 1 will test if African ancestry (%AF) is associated with short SWS duration and poor SWA in older AAs. Challenge: AAs consistently spend less time in SWS than whites[23-32]. Although SWS shows significant heritability, social stressors may moderate these differences. Approach: test whether %AF[40] is associated with SWS characteristics after controlling for psychosocial factors (*e.g.* stress related to ethnicity). Outcome: positive results would suggest that racial differences in SWS have genetic underpinnings.

Aim 2 will test the effect of race and its interaction with baseline short SWS duration/poor SWA on longitudinal amyloid deposition. Challenge: AAs spend less time in SWS[23-32], a sleep stage important for Aβ dynamics[41-43] that may confer protection against amyloid deposition[44]. Approach: assess how race is associated with longitudinal PiB uptake and its interaction with short SWS duration and poor SWA, after controlling for: 1) medial prefrontal (mPFC) atrophy, TST, AHI4% and cerebrovascular damage (measured as white matter lesion [WML] volume and abnormal diffusion kurtosis imaging [DKI] indices); and, 2) psychosocial factors, health care behaviors and medical morbidity. Outcome: reduced SWS/SWA would become a novel risk factor for AD in African Americans (AAs).

Aim 3 will test the effect of race and baseline poor SWA on cognition. Challenge: race and poor sleep have been associated with cognitive impairment. However, most studies are confounded by the inclusion of OSA patients, subjective measurements of sleep, lack of valid cognitive assessments for AAs and inadequate enrollment of minorities. Approach: we will test for the association between race and longitudinal changes in global cognition, memory, executive function and a sleep-dependent spatial navigational memory task. In addition, we will test their interaction with baseline SWA, using a similar approach as in Aim 2. Outcome: positive results would emphasize the importance of health messages promoting good sleep hygiene among AA elderly.

3.2 Secondary Objectives (if applicable)

Secondary Objective : Exploratory: we will test whether loss of sleep-dependent spatial navigational memory at baseline is a predictor of cognitive decline at follow-up. A linked objective is to identify how the relationship between SWS/SWA and the rate of change in PiB uptake might be confounded by mPFC atrophy (for measures of SWS) and DWML volumes and DKI (for measures of PiB uptake).

4 Study Enrollment and Withdrawal

Subjects:

210 cognitively normal, ages 60-75, self-identified as African-American (150) or non-Hispanic white

(60), Clinical Dementia Rating (CDR) of 0, ≥-1.25 in global cognition z-scores from the WHICAP battery adjusted for race and education, English speakers, and with enough literacy to provide voluntary consent will be invited to participate.

Exclusion criteria at enrollment will be: intention to move from NYC within the same year, irregular sleep-wake cycles defined as '≥3 sleep episodes per 24-hr period' or 'day to day irregularity greater than 90 min. based on actigraphy, less than 5 or more than 10 hours of TST; OSA (defined as AHI4%>15 and AHI4%>5 with Epworth≥10); neurodegenerative disorders, history of early onset familial AD; insulin dependent diabetes; bipolar disorder, schizophrenia, intellectual disability or substance abuse; non-controlled pulmonary or cardiac diseases; brain tumors; stroke; head trauma and hydrocephalus.

Lifelong depression and anxiety will be allowed as long as there has been no active depressive episode within the last two years. Current use of any sedative/hypnotics or stimulants, gabapentin, pregabalin, tricyclic antidepressants, and trazodone or other psychoactive medications that may alter SWS. Stable (3 months or longer) use of antidepressants will be allowed. Caribbean or African-born blacks or subjects that don't fulfill inclusion criteria but express interest will be offered participation in similar NYU NIH-funded studies on sleep or normal aging.

Study Enrollment:

Self-identified AA and whites will be balanced by sex, age, BMI, income and education, and will live in the same NYC zip codes. Brooklyn will be the area of recruitment as it is the most ethnically diverse and largest most concentrated black population in the US -more than 900,000 blacks living in a 4-mile square area-. The sample will include self-identified African-American (AA) blacks and non-Hispanic whites. As described in our published methods[158;166], enrollment sites will include advertisements and collaborations with black-owned barbershops, beauty salons and churches that were part of our previous community studies in Brooklyn and other NYC boroughs. All advertisements and recruitment materials will be submitted for IRB approval prior to use. In addition, we will perform culturally-relevant educational events in senior centers and church health fairs. Recruitment will be implemented in consultation with a Community Activist (Ms. Aird) and a Community Advisory Board (CAB) that has been created for this cohort. It will include community stakeholders with whom we have long-standing relationships and consist of: black community leaders serving as Directors of Community-based organizations (CBOs) and members of the Brooklyn chapter of *CaringKind*. The CAB will comprise 8 members and will meet with the PIs and Dr. Galvin, who will be one of the lead members of the community advisory board every 2 months during year 1 and every 3 months thereafter. Once the award is made, it will discuss project goals, review recruitment strategies, refer individuals for participation and suggest new recruitment sites that might not have been available previously. Our success in assessing sleep in AAs is attributable to our sustained engagement efforts at the community level and help from former CABs.

Participating recruitment sites will be selected based on visibility, accessibility, safety, longevity and cooperativeness[204]. Preference will be accorded to those providing private room for interactions with subjects. Recruitment procedures will be discussed with site owners before scheduled visits. Respective owners will introduce the recruitment team, who will then approach potential participants (while waiting at the salon, after church services or senior center activities) to describe the protocol. The recruitment team will be made up of research coordinators and other members of the study staff. As in our previous interventions[158], staff will begin by exchanging pleasantries with potential participants followed by an introduction to the study.

If interested, eligibility will be confirmed and consent obtained. They will then complete the Center for Epidemiologic Studies Depression (CES-D)[205] Scale, the Medical Outcomes Study Short Form (MOSSF)[206], the ARES-TM questionnaire[149], a medication list and the AD8[207] (these forms will be used for initial screening; interested subjects not eligible or with high risk for OSA will be offered participation in similar NYU NIH-funded studies). Those refusing to enroll will receive standard sleep literature and access to the NYU ADC Center or Brooklyn's NYU affiliated Lutheran Medical Center. No further contact will be made. During the first 9 months, themes derived from focus groups (*R01MD004113*) and through meetings between the PIs, Dr. Galvin and the CAB will be used to develop sleep and memory health booklets using Taylor's model[208]. These booklets will be left on the participating centers for recruitment outside the scheduled visits. All recruitment materials will be submitted to the IRB through a modification for approval

before use.

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Male and female subjects with normal cognition and ages 60 to 75.
- Within normal limits on neurological and psychiatric examinations. All subjects enrolled will have both a CDR=0, a MoCA > 25 and ≥-1.25 in global cognition z-scores from the WHICAP battery.
- An informed family member or life-partner (preferably bed-partner) will be interviewed over the phone or on the first or second visit to confirm the reliability of the subject interview. A study partner is preferably a spouse, close friend, or relative.
- Self-identified as African-American Black or non-Hispanic white.
- All subjects must sign the Alzheimer's Disease Center consent form

4.2 Exclusion Criteria

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

- History of brain tumor, MRI evidence of brain damage or brain disease including significant trauma, hydrocephalus, seizures, mental retardation or other serious neurological disorder (*e.g*. Parkinson's disease or other movement disorders). Subjects with a Fazekas scale >2 will be excluded[260].
- Significant history of alcoholism based off of the CAGE questionnaire (>2) or drug abuse.
- History of psychiatric illness (*e.g*., schizophrenia, bipolar or PTSD
- Lifelong depression and anxiety will be allowed as long as there has been no active depressive episode within the last two years.
- Geriatric Depression Scale[212] (short form)>6.
- Insulin dependent diabetes.
- Evidence of clinically relevant cardiac, pulmonary, endocrine or hematological conditions based off of the PI's discretion.
- Physical impairment of such severity as to adversely affect the validity of psychological testing.
- Any prosthetic devices (*e.g.,* pacemaker or surgical clips) that constitutes a hazard for MRI imaging.
- Medications affecting cognition or SWS:
    - Narcotic analgesics.
    - Chronic use of medications with anticholinergic activity.
    - Anti-Parkinsonian medications (carbidopa/levodopa, amantadine, bromocriptine, pergolide, selegiline).
    - Others: amphetamines, amphetamine-like compounds, appetite suppressants, phenothiazines, reserpine, buspirone, clonidine, disulfiram, guanethidine, MAO inhibitors, theophylline, tricyclic antidepressants, gabapentin, pregabalin, trazodone, cholinesterase inhibitors, memantine.
- Chronic use of antidepressants are allowed.
- History of a first-degree family member with early onset (age <60 years) dementia.
- Irregular sleep-wake rhythms (based on participant self-report), short sleepers (< 5 hours a day) and long sleepers (> 10 hours a day).
- OSA (defined as AHI4%>15 and AHI4%>5 with Epworth≥10)
- Self-identified as US-born Caribbean Black, Caribbean-born Black or African-born Black.

Diagnostic Criteria:

1. <u>The diagnoses of MCI, and AD</u>. All subjects get extensive baseline and follow-up evaluations to identify co-morbidity and any confounding medical, neurological, and psychiatric conditions that can affect cognition. For all subjects, the study neurologist or psychiatrist administers a standardized interview of a knowledgeable informant. The diagnosis is assigned at consensus case conferences using established and reliable procedures. The following diagnoses might be given at follow-up:

b. **The definition of MCI:** subjects demonstrating functional complaints (self-reported and supported by a knowledgeable informant) and who on clinical interviews show no dementia but with a CDR=0.5, GDS =3, and MOCA <25 are classified as MCI. Amnestic (a) aMCI is defined on the basis of updated. Petersen criteria with delayed recall performance below 1.5 SD from age norms on 2 of the 3 tests within the delayed recall domain. Prior experience shows that the aMCI will likely also show deficits in other cognitive domains. The category of non-aMCI is defined based on performance on more than one cognitive test from a domain other than delayed recall, falling below z=1.5 SD from the norms (see below). Subjects judged to be cognitively impaired by the clinician, but with a presentation, tests, symptoms and clinical evaluation that is not consistent with MCI will be classified as 'Impaired, not MCI'.

c. **The diagnosis of AD**: at the follow-up is consistent with the NINCDS-ADRDA workgroup recommendations and DSM IV criteria. The definition of AD requires that after ruling out other dementia etiologies that the individual demonstrate on structured clinical interviews, progressive impairments in two or more areas of cognition and difficulties in activities of daily living. Thus AD is rated as CDR >0.5. The memory impairment criterion is satisfied by scores in the impaired range on any of the delayed recall tests in the neuropsychological battery. Functional impairment is estimated by scores on the Lawton Brody Activities of Daily Living Scale, the clinical history evaluation, and the informant interview.

4.3 Vulnerable Subjects

We are not including children or women who are pregnant because this study is designed for adults and elderly subjects.

4.4 Strategies for Recruitment and Retention

Expected Participant Flow:

Yearly complete evaluations (including baseline and follow-up) will range from 80-84 (Table 2). Initial screening will be performed through the CES-D, MOSSF, ARES-TM, medication list and AD8. The number of total subjects enrolled will be of 270 to meet the goal of 210 eligible subjects. We anticipate that 17% will be referred to seek treatment due to OSA, while 3-5% will not complete the study evaluations or fulfill inclusion criteria due to cognitive impairment. Based on an average of 24 hours of contact time for each subject (6 h for visits 1-2, 18 h for night 1-2) we will be able to complete 2 subjects per week. To maximize cohort retention we will adopt strategies developed for our own studies[209-211] and more than 20 years of experience working with underrepresented groups at the NYU ADC. These will include: *i*) a multicultural staff; *ii*) providing flexible visit options; *iii*) using monetary incentives after completion of all study visits (each subject will receive $500 after a completed milestone and payment is not contingent upon completing all visits); *iv*) making reminder phone calls prior to scheduled visits; *v*) providing a clinical report to share with their primary care physician; *vi*) sending Annual Holiday letters; *vii*) performing telephone follow-ups after completion of the baseline visit; and, *viii*) participating in local memory walks in Brooklyn together with the *Alzheimer's Association,* and co-sponsoring together with the NYU ADC three annual scientific updates at NYU's Langone Medical Center in both English and Spanish. Previous annual attrition rates at the ADC have been 4% for healthy controls, 13% for MCI and 20% for AD patients. We anticipate that the efforts described above will lead to even higher retention rates (expected 95% at the 2.5 year follow-up)

4.5 Duration of Study Participation

The study will be over the course of 30 months per participant, although we will provide flexible visit options and up to 35 months will be allowed.

4.6 Total Number of Participants and Sites

Up to 270 people will be enrolled to reach a goal of 210 evaluable participants (accounting for attrition).

4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

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

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation during the 2-year follow-up.

4.7.2 Handling of Participant Withdrawals or Termination

For a variety of reasons, subjects may decide to withdraw from the study, or the PI may decide to terminate a subject's participation regardless of whether the subject wishes to continue participating. Data collected on the subject to the point of withdrawal will remain part of the study database and will not be removed. The consent document will give the subject the option of having his/her data anonymized. In all cases we will ask subjects who are withdrawing whether they wish to provide continued clinical follow-up subsequent to their withdrawal (*i.e.* yearly clinical interview by Dr. Butler and neuropsychological evaluations that are part of the UDS-3). Under this circumstance, the discussion with the subject will distinguish between study-related evaluations and continued follow-up of associated clinical outcome information, such as medical course obtained through a clinical interview and neuropsychological tests. A second option will be to continue participation through the ADC cohort. In all cases we will address the maintenance of privacy and confidentiality of the subject's information.

If a subject: *i*) withdraws from the study, *ii*) does not consent to continued follow-up of associated clinical outcome information, and *iii*) does not request removal of their data, the PI will not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, the PI may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status. A subject will be considered lost to follow-up after non-response to: 5-10 phone calls to the telephone number provided by the subject, 5 phone calls to the study partner, 3 emails and 1 certified letter to the participant home address. Replacement will be allowed in those subjects that withdraw from the study in less than 12 months after the baseline visit.

4.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

5 Study Schedule

5.1 Screening

Screening Visit (Day 0)

- Obtain verbal consent from potential participants.
- Fill out the following forms: Center for Epidemiologic Studies Depression Scale (CES-D), Medical Outcomes Study Short Form (MOSSF), ARES-TM Questionnaire
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for individuals who are eligible and available for the duration of the study.
- Provide potential participants with instructions needed to prepare for first study visit

5.2 Enrollment/Baseline

Enrollment/Baseline Visit 1 (Visit 1, Day 1)
This visit will occur at the Center for Brain Health (CBH) 145 E. 32nd Street, 2nd Floor

- Obtain and document consent from participant on study informed consent form (ICF).
- Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
- Clinical evaluation and record results of physical examinations
- Collect blood and urine for clinical labs and in order to obtain ApoE genotyping
- Perform EKG
- Administration of the clinical section of the UDS 3.0 cognitive evaluation
- Administration of the WHICAP cognitive battery
- Verify inclusion/exclusion criteria after clinical interview, clinical labs and neuropsychological tests.
- Participants will receive a one week sleep diary, WatchPAT to wear for 1 night and an actigraph to wear during the remaining 7 days of the week.

Baseline Visit 3 (Visit 2, Night 1/Day 2)

This visit will occur at the Mount Sinai Integrative Sleep Center (MSISC) 11 E 26th Street, 13th Floor

- Nocturnal Polysomnography at their usual bedtime
- Provide actigraphy device to monitor naps and compliance with the instruction to not sleep between visits while at home.
- Provide breakfast.
- Subjects can go home for the day.

Baseline Visit 4 (Visit 3, Night 2/Day 3)
This visit will occur at the Mount Sinai Integrative Sleep Center (MSISC) 11 E 26th Street, 13th Floor

- Virtual maze spatial navigational memory test training session.
- Nocturnal Polysomnography.
- Virtual maze spatial navigational memory test testing session.
- Provide breakfast

Baseline Visit 5 (Visit 4, Day 4)

- *This visit will occur at the Center for Brain Health and the Center for Biomedical Imaging (660 1st Avenue at E. 38th Street)* Complete UDS 3.0 Cognitive evaluation and sleep interview at the Center for Brain Health

- PiB PET-MR Scan: PiB PET-MR scan of your brain at the Center for Biomedical Imaging (Pregnancy urine test will be done on women prior to the exam)
    - PET/MR scans combine two types of imaging methods: Positron Emissions Tomography (PET) and Magnetic Resonance Imaging (MRI). PET uses radioactive tracers to produce images that can inform us how a particular compound is used by tissue or for identifying unique cell-types, such as Tau, in this study. MRI uses magnetic fields and radio waves to produce images that can inform us about structures and function of tissue in the body. Combining both techniques provides more useful information while reducing the amount of radiation exposure compared to a standard PET scan or PET/CT. A small amount of tracer known as ^{11}C-Pittsburgh compound-B (PiB) will be injected into a vein in your arm before the scan begins and a 60-min PET-MR scan will be performed 35 min after injection.

Followup Study Visit

12-Month Follow-Up Visit 1-day visit
This visit will occur at the Alzheimer's disease Center (ADC) 145 E. 32nd Street, 2nd Floor

- UDS 3.0 cognitive evaluation will be re-administered by Alzheimer's Disease Center clinicians and testers
- You will have a physical, neurological, and psychiatric examination along with collection of vital signs (heart rate, blood pressure, temperature, and breathing rate) and medical history including medications you take and surgeries you have had.
- Electrocardiogram (EKG): Assesses the electrical activity of your heart. Electrodes (sensors connected to wires on the EKG machine) will be attached to your chest, upper arms, and legs. The heart tracing will take approximately 10 minutes to complete.
- You will have a urinalysis for routine testing to screen for urinary infections.
  Blood will be drawn for clinical labs and to obtain DNA for ApoE genotyping (Baseline Visit 1 only). The total amount of blood to be donated for the baseline and follow-up visits up the study is equivalent to approximately 6 tablespoons of blood.
  No MRIs or additional procedures will be perfomed in the 12 month fu visit

30-month Follow-Up Visit 1 (Visit 1, Day 1)
This visit will occur at the Center for Brain Health (CBH) 145 E. 32nd Street, 2nd Floor

- Obtain demographic information, medical history, medication history, alcohol and tobacco use history
- Clinical evaluation and record results of physical examinations
- Collect blood for clinical labs
- Perform EKG
- Administration of the clinical section of the UDS 3.0 cognitive evaluation
- Administration of the WHICAP cognitive battery
- Verify inclusion/exclusion criteria after clinical interview, clinical labs and neuropsychological tests
- Participants will receive a one week sleep diary, and an actigraph to wear during the week.

30-month Follow-Up Visit 2 (Visit 2, Night 1)
This visit will occur at the Mount Sinai Integrative Sleep Center (MSISC) 11 E 26th Street, 13th Floor

- Nocturnal Polysomnography at their usual bedtime
- Provide actigraphy device to monitor naps and compliance with the instruction to not sleep between visits while at home.
- Provide breakfast.
- Subjects can go home for the day.

30-month Follow-Up Visit 3 (Visit 3, Night 2/Day 3)
This visit will occur at the Mount Sinai Integrative Sleep Center (MSISC) 11 E 26th Street, 13th Floor

- Virtual maze spatial navigational memory test training session.
- Nocturnal Polysomnography.
- Virtual maze spatial navigational memory test testing session.

- Provide breakfast.

30-month Follow-Up Visit 4 (Visit 4/ Day 4) *This visit will occur at the Center for Brain Health and the Center for Biomedical Imaging (660 1st Avenue at E. 38th Street)* Complete UDS 3.0 Cognitive evaluation and sleep interview at the Center for Brain Health

- Complete UDS 3.0 Cognitive evaluation
- PiB PET-MR Scan

5.3 Withdrawal Visit

For a variety of reasons, subjects may decide to withdraw from the study, or the PI may decide to terminate a subject's participation regardless of whether the subject wishes to continue participating. Withdrawal visit will consist in one day and the schedule of procedures will be the same as in Intermediate Visit 1. If the participant refuses to come to Center for Brain Health, the clinician will perform a clinical interview over the phone.

6 Study Procedures/Evaluations

6.1 Procedures/Evaluations

Clinical evaluation: all subjects will perform a standardized clinical evaluation (UDS 3.0) given to all participants seen at the NYU ADC. The purpose of this clinical evaluation is to establish that subjects are cognitively normal, identify concurrent medications that may act as confounders (*e.g.*, benzodiazepines, trazodone, suvorexant), increase reproducibility of the clinical evaluation, and facilitate collaborative research with NACC (see *Resource Sharing Plan*). Depressive symptoms will be measured using the Geriatric Depression Scale (GDS)[212;213]. We will add information about: health insurance, annual household income, perceived discrimination (Index of Race-Related Stress [IRRS]-Brief Version B[214]), the Weinstein Noise Sensitivity Scale (WNSS)[215], the Perceived Stress Scale (PSS)[216] and the SF36 health behaviors survey[217] to control for environmental, health and psychosocial factors that might disrupt sleep. In addition, all subjects will undergo complete fasting blood tests (CBC with differential and platelet count, highly sensitive CRP, ESR, total T3 and T4*, lipid profile, RPR*, comprehensive metabolic profile with insulin, folate*, homocysteine*, and vitamin B12*, SMA-18, HbA1c, hemogram)). Subjects will then complete the WHICAP battery and the AMNART test[4]. The tests comprising this neuropsychological battery were chosen because unlike the UDS 3.0, they have race-specific norms[5]. We will construct three composite scores for general cognition, memory, and executive function from factor analyses. We will use total recall, delayed recall, and delayed recognition from the Buschke Selective Reminding Test[218] to construct the memory composite. The executive functioning composite will be created using the Color Trail-Making Test (A and B)[219], WAIS-R (Wechsler Adult Intelligence Scale-Revised), Similarities, Identities/Oddities subtest of the Mattis Dementia Rating Scale[220], two cancellation tasks and semantic fluency for animals[221]. All of the above variables, together with phonemic fluency[221], the 15-item Boston Naming Test[222], repetition task (high-frequency phrases of the Boston Diagnostic Aphasia Examination[BDAE][223]; and a comprehension task, will contribute to the composite for general cognition. Means and standard deviations (SD) will be calculated from baseline scores for non-demented WHICAP subjects controlling for age, race and years of education using robust norms. Z-scores for each of the cognitive measures will be averaged to create a composite z-score for each of the three domains. Only subjects diagnosed as cognitively normal with a z-score >-1.25 SD of the mean in general cognition will be invited to participate. The time to complete the WHICAP test battery will range from 45-90 min. On visit 2, prior to the PET/MR scan, subjects will complete the UDS 3.0 cognitive evaluation to facilitate collaborative research with NACC.

Ambulatory home monitoring for OSA followed by actigraphy:

Subjects will be asked to monitor their sleep using sleep logs during one week. On the first night, OSA will be monitored using a WatchPAT (*Itamar Medical, Tel Aviv, Israel)* (Figure 8). We have experience using WatchPAT in AAs with very low failure rate (less than 1%). This self-applied device measures peripheral arterial volume changes using a finger-mounted plethysmograph. The information is collated

with pulse oximetry and is further analyzed using an automated algorithm. This algorithm associates arousals with measurement of O_2Sat to determine respiratory effort-related arousals showing excellent sensitivity and specificity for identification of OSA, defined as AHI4%≥5 on full NPSG[224]. After automated analysis, all raw data and results are reviewed by Dr. Ayappa. Only subjects with an AHI4%<15 and AHI4%>5 with Epworth<10 will be invited to participate. Those cases with suspicion of OSA will be reviewed by Dr. Rapoport and Varga. If OSA is confirmed, they will be excluded and referred to a sleep specialist. Actigraphs (*AMI, Ardsley, NY*) (Figure 9) with off-wrist detection and a sleep diary will be provided to the subjects to use for the 7 days following the use of the WatchPAT. The purpose will be to record the sleep-wake cycle and provide estimates of total sleep time (TST) in the home. Actigraph will also provide bedtimes and wake times for NPSG N1-N2 in accordance with their usual sleep habits.

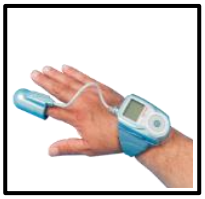


Figure 8. WatchPAT

Figure 9. Actigraph

Measurement of Slow Wave Sleep (SWS) characteristics using NPSG:

Each in-lab NPSG will record sleep as recommended by the AASM[225] as described in our previous work[156]. Electrode attachment will be performed between 8-9 PM. Subjects will be then asked to sit quietly and/or read until lights out at their habitual bedtime. NPSG N1 will be for habituation, N2 will be for data collection. Arousal index (AI), sleep staging, TST, sleep efficiency and wake after sleep onset (WASO) during NPSG will be scored by one trained technologist blinded to PET data using standard AASM criteria[225]. Participants will go home between N1-2 provided that they wear the actigraph with off-wrist detection, avoid naps or exercise and track their meals. SWS will be scored visually as: 1) TST in SWS in min. (SWS duration); and, 2) %TST spent in SWS (%SWS). SWS measurements will be measured in N2. In addition, we will include: 1) slow wave activity (SWA): absolute SWA (defined as power between 0.5-4.0 Hz during NREM), relative SWA (SWA divided by power across all 0.4-50 Hz). NREM cycles will be defined as stages NREM2-3 of ≥15 min. terminated by REM or wakefulness of ≥5 min. Delta power will be averaged relative to the number of epochs. 2) SWS continuity: bouts of SWS will be defined as the duration of consecutive 30 sec. epochs of sleep scored as SWS, terminated by one or more epochs scored as another stage as described in our previous work[226;227].

Sleep-dependent Neuropsychological Tests:

On NPSG N2, participants will be trained in our published 3-D virtual maze spatial navigational test (see Figure 10)[141;156] Navigational memory represents a good model to study the effects of sleep-dependent memory consolidation. Rodent studies show that patterns of firing in hippocampal place cells during wake are replayed both in REM[228] and NREM[229] sleep. Behaviorally, sharp-wave ripple suppression impairs performance on a radial arm maze,[230] while REM suppression impairs memory in the radial arm maze[231] and in the Morris water maze[232]. In humans, overnight sleep enhances virtual maze navigation performance[233;234], while we have shown that maze completion time (CT) is attenuated after REM disruption[176] and is correlated with SWA in elderly subjects[188]. Subjects will experience two different mazes at baseline and at the 2.5-year follow-up, and mazes will be counterbalanced across subjects for which maze is experienced first. Both mazes have been designed such that optimal CT is equivalent assuming perfect knowledge of the maze layout. Maze performance will be expressed as % change across sleep in maze CT compared to baseline CT before sleep. We have chosen a maze over a word-pair test[105;235;236] because: 1) it taxes the hippocampus (more than a word-pair tasks would); 2) it's ecologically relevant to AD (*i.e.* spatial disorientation is one of the early clinical AD-symptoms); and 3) there are equivalent rodent models that lend insight into the underlying electrophysiological mechanisms (*i.e.* sharp-wave ripples, which cannot be captured with surface EEG).

Figure 10. Bird's eye view of virtual maze

PiB PET and MRI scans:

On visit 4, baseline and follow-up subjects will receive a single dose of 11.12 mCi PiB and perform a dynamic 60 min amyloid PiB PET-MR scan 35 min after injection.. The radioactive drug (PiB) shall meet appropriate chemical, pharmaceutical, and radionuclidic standards. The dose will be radioassayed proper to administration to ensure dosimetry data is correct. Further, the mass of the PiB is not expected to produce a pharmacologic response. PET/MR scans will be performed on an integrated 3T PET/MR

(*Siemens Biograph mMR, software Syngo MR B18P*). For anatomic coregistration, a sagittal 3-D MPRAGE sequence will be performed (208 slices, 1mm isotropic voxels). Attenuation correction will be performed using a Dixon μ-map with a superimposed bone compartment and linear AC developed at NYU[237]. Modifying the linear AC value and superimposing a model-based bone compartment reduces the whole-brain SUV estimation bias of Dixon-based PET/MR AC by 95% compared with reference PET/CT AC ($p<.05$), resulting in a residual −0.3% SUV mean bias[237]. Ultrashort echo time (UTE) will also be acquired and combined to the Dixon μ-map to incorporate the bone tissue[238]. Simultaneous PET-MR acquisition eliminates the need of registering the PiB images to MNI. Instead, we will use the MPRAGE for registration, which offers a fine volumetric resolution and high contrast ratio required to precisely differentiate between GM and WM. For each patient, the MPRAGE image will be automatically segmented into, neocortical and cerebellar hemisphere GM regions of interest (ROIs) using *FreeSurfer*. These GM neocortical ROIs will be collapsed to yield four large volume-weighted ROIs that span prefrontal, lateral temporal, parietal cortex and anterior/posterior cingulate gyrus cortices (as described in[239]). An AD_{PiB}mask index will be the primary variable of interest in this study, derived by averaging these mean SUV values to a reference region containing the supratentorial WM and whole cerebellum. PiB+ will be defined as a AD_{PiB}mask ≥1.4. The combined region will be used to calculate longitudinal estimates of change in PiB uptake.

Images for exclusion and structural brain measurements of middle prefrontal cortex (mPFC). Along with the PET acquisition we will acquire several sets of images intended to screen for brain disease, stroke or extensive white matter lesions. We will we use a thin slice 3D sagittal T1 MPRAGE sequence. Parameters are: TR 2100 ms; TE 4.37 ms; TI 900 ms; flip angle 8°; matrix 240 (read) x 256 (phase) x 208 (partitions); FOV 256 (read) x 192 (phase) x 240 (partitions) mm; iPAT 2; voxel size 1.0x1.0x1.0 mm; NEX 1; acquisition time 4.35'. Whole brain and cortical volumes: automatic brain segmentation, cortical surface reconstruction and parcellation will be performed using *FreeSurfer* (surfer.nmr.mgh.harvard.edu). Segmentations will undergo qualitative reviews and volumes will be residualized to intracranial volume (ICV)[169].

Fluid-attenuated inversion recovery (FLAIR): We will obtain complete brain coverage using 3D sagittal FLAIR SPACE sequences to quantify white matter lesions (WML). Parameters are: TR 6000 ms; TE 325 ms; TI 2100 ms; matrix 256 (read) x 248 (phase) x 176 (partitions); FOV 256 (read) x 248 (phase) x 176 (partitions) mm; iPAT 2; voxel size 1.0x1.0x1.0 mm; NEX 1; acquisition time 2.56'. WML volume (mL) is considered a surrogate marker of small vessel disease.[240] It will be obtained using an semi-automatic approach based on hyperintense (≥mean+2.5SD) voxels in WM with our locally developed software *FireVoxel*[241;242] (files.nyu.edu/hr18/public). WML volume will be subdivided into periventricular (PWML) and deep (DWML).

Diffusion Kurtosis Imaging (DKI) is an extension of diffusion tensor imaging (DTI)[243] that provides the information obtained from DTI, plus additional non-Gaussian diffusion parameters,[244] as well as new WM tract integrity (WMTI) metrics[245;246] that are specific to underlying pathology: (a) axonal water fraction (*marker of axonal density);* (b) D_{axon}, diffusivity inside the axons (*marker of axonal injury);* and (c) $D_{e||}$ and $D_{e\perp}$, extra-axonal axial and radial diffusivity (*markers of extracellular inflammation, gliosis and demyelination).* We will use an optimized protocol in terms of number of shells (b-values) and encoding directions, providing the best coverage of q-space for diffusion and kurtosis tensors estimation within a short acquisition time (~7 min). The protocol can be summarized as follows: TR 8200 ms; TE 96 ms; b=0 (4 averages), b=250 (6 directions), b=1000 (20 directions), b=2000 (30 directions), s/mm², b=0 with reversed phase encoding direction (1 average); 50 axial slices; FOV 230 (read) x 230 (phase) mm²; voxel size 2.5x2.5x2.5 mm³. The DKI data will be used to derive parametric maps of DTI and DKI, followed by derivation of WMTI maps using our in-house developed processing pipeline (github.com/NYU-Diffusion MRI/Diffusion-Kurtosis-Imaging). Next, all maps will be transformed into standard space using FMRIB's Software Library. Mean values will then be extracted for each metric to assess the microstructural WM damage beyond lesions visible on FLAIR.

Individual Genetic Ancestry Estimation

Allele frequencies will be ascertained from Utah residents with Northern and Western European ancestry and West African (Yoruban from Nigeria) samples available in the HapMap database. Individual % African ancestry (%AF) estimates from 0-100 will be computed using a maximum likelihood method for inferring individual admixture[247]. Briefly, an algorithm is used to compute the probability of observing a marker genotype given ancestral allele frequencies at a locus. Summing over the logs of individual locus probabilities combines information across multiple loci. The admixture proportion that maximizes the

probability of obtaining the observed genotype is the maximum likelihood estimate of ancestry for the individual[199;248].

6.2 Laboratory Procedures/Evaluations

SOURCES OF MATERIALS:

The raw data collected in the current proposal will include MRI and PET scans, blood samples for DNA genotyping, neuropsychological test scores, and clinical data from medical, neurological, psychiatric exams, sleep, cardiologic and respiratory evaluations. Only approved study personnel will interact with participants and have access to subject information. Data will be collected during full-day in-home and nocturnal in-laboratory (polysomnography) sleep studies that are standard clinical practice. Medical records will be kept in accordance with state and federal laws concerning the privacy and confidentiality of medical information. All efforts will be taken to maintain subject confidentiality and research will be conducted following good clinical practices. Each subject will be assigned a unique code number. Confidentiality will be maintained by keeping paper study data in a locked drawer in a locked office. All electronic data will be stored on the Mount Sinai Integrative Sleep Center (MSISC) and NYU Center for Brain Health (CBH) databases such as RedCap, which are password protected and stored within the secure Mount Sinai Medical Center Information Technology (MSMCIT) and NYU Langone Medical Center IT (NYULMCIT) systems. Data will only be available to the key personnel. All have taken HIPAA and IRB tutorials.

6.3 Study Specific Biospecimens

6.3.1 Specimen Collection Procedures

Collection of Blood. We will collect blood at Visit 1 for the baseline and follow-up visits to perform clinical labs and 10 ml of fresh blood to extract DNA (only at the baseline visit) the total amount of blood for both baseline and follow-up visits will be approximately 80cc's. The fresh blood samples will be sent to LGC Genomics where DNA will be extracted and sent back to NYU after GWAS analyses. All data regarding DNA samples will be entered into the ADC-CBH database for sample tracking. While a sample is being processed, one back-up sample with fresh blood will be maintained.

6.3.2 Specimen Preparation, Handling, and Storage

6.3.2.1 Supplies:

-
- 2 PaxGene blood DNA tubes (catalog number 761115)
- 3 purple-topped tubes,1 red-topped tube, and 2 gold-topped tubes
- 27 Nalgene™ General Long-Term Storage Cryogenic Tubes (Fisher catalog number 5000-0020).

6.3.2.2 General blood handling considerations:

The release of cellular material due to hemolysis into the serum or plasma may introduce additional confounding factors in downstream analysis of such samples. When hemolysis is observed (pink to red tinge in sample that persists after one cycle of centrifuging), this information will be recorded in the plasma/serum (PS) log

6.3.2.3 Serum handling considerations (red topped tubes)

Serum samples should be left at room temperature at least 30 minutes. If the subject is taking any kind of anticoagulant or blood thinner (warfarin, factor Xa inhibitors, heparin, thrombin inhibitors, antiplatelet drugs) (variable name '*anticoag_meds*') at the time of sample collection, leave at least 45 minutes. Check

if the clot has formed at 45 and 60 minutes. Record this information in the plasma/serum log (variable '*clot time in minutes*'). Steps:

- Check medication list provided by the subject.
- Record any kind of anticoagulant or blood thinner in the PS log
- Record time of blood draw in the PS log.
- Allow blood to clot for a minimum of 30, 40, or 60 minutes in a vertical position at room temperature.
- Observe a dense clot.
- Record time of centrifuge start in the PS log.

6.3.2.4 Plasma Handling Considerations (lavender topped EDTA tubes)

The volume of blood collected in each tube and adequate mixing of the sample into the additive are critical steps.

- Record time of blood draw in the PS log.
- Fill tubes.
- Gently invert tubes 8-10 times.
- Centrifuge at the same time as the serum.

6.3.2.5 Temperature and Light:

Protect samples from extreme temperatures. Transport with icepacks on the sides. Make sure icepacks are never in direct contact with the samples. Do not place blood tubes in windows as direct sunlight can cause the red cells to lyse, and may impact the usability of the specimen.

6.3.2.6 Processing:

- Put 1cc of whole blood from purple tube in two small vial for genetics (vials GEN1-2)
- Heat centrifuge to 21 degrees.
- Spin bloods on at 3000 RPM during 15 minutes.
- Aliquot EDTA plasma into vials PLM1-10. *(1.5cc per vial.)*
- Aliquot EDTA WBC (buffy coat) into vials WBC1-2. *(0.5 cc per vial.)*
- Aliquot serum into vials SER1-4. *(1.5 cc per vial.)*
- Put samples into cryogenic box.
- Transport box to -80C with icepacks on the side.

6.3.3 Specimen Shipment

Specimen Shipment:

Specimens will be shipped on dry ice for DNA extraction and ApoE4 genotyping to LGC Genomics for DNA extraction (LGC, 100 Cummings Center, Suite 420H, Beverly, MA 01915, US) and NCRAD once a year. Samples will include the 4 digit subject ID only.

6.4 Questionnaire Administration.

All questionnaires are part of the clinical evaluation and are included as addendums

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Unanticipated Problems Involving Risk to Subjects or Others:

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (*i.e.* not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.).

- Related or possibly related to participation in the research (*i.e.* possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

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- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation should be recorded and reported immediately.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.3.1 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events* that are unexpected and related**
  - *<u>Unexpected</u>: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*

- *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
- *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using a Reportable New Information submission and will include a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution, and need for revision to consent form and/or other study documentation. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8 Study Oversight

It is the responsibility of the Principal Investigator (Dr. Osorio) to oversee the safety of the study alongside with the Co-Investigator (Dr. Jean-Louis). This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The PIs will work to develop all aspects of the proposed study including direct oversight, staff supervision, engagement of the Community Advisory Board (CAB), supervision of staff, enrollment and monitoring of eligible participants, acquisition and management of subjective and clinical data, analysis and dissemination of study results. They will also ensure that stated aims are achieved in a timely manner. Moreover, each PI will focus on different but related aspect of the specific aims based on their primary expertise.

9 Statistical Considerations

9.1 Study Hypotheses

1. Hypothesis 1.1: poor SWS characteristics (short SWS duration, low %SWS, low relative SWA, low SWS continuity and high AI) at baseline will be associated with high %AF. Hypothesis 1.2: psychosocial factors (*e.g*. perceived discrimination) will partially moderate the above relationships.
2. Hypothesis 2.1: race will be associated with longitudinal increases in the annual rate of AD_{PiB}mask change. Hypothesis 2.2: the effect of race in terms of longitudinal increases in AD_{PiB}mask will be partially explained by poor relative SWA at baseline.
3. Hypothesis 3.1: race will be associated with longitudinal changes in global cognition, memory, executive function and sleep-dependent spatial navigational memory. Hypothesis 3.2: the association of race in terms of cognitive decline will be partially explained by poor relative SWA at baseline. Exploratory Hypothesis: absence of improvement in sleep dependent memory consolidation at baseline will be associated with longitudinal decreases in global cognition, memory and executive function.

9.2 Sample Size Determination

Power was assessed under the assumption that dropout replacement will allow complete data to be acquired from 200 subjects. Based on the existing literature[23-32], the coefficient of variation (CV) of SWS duration is anticipated to be as high as 90% among AA and 40% among whites. Baseline data from 150 AA and 60 whites will therefore provide 80% power at the 5% significance level to detect a mean SWS duration among whites that is at least 28% higher than among AA. Based on PD4, the CV of PiB uptake at baseline is anticipated to be as high as 35% among AA and 25% among whites, providing 80(90)% power at the 5% significance level to detect a mean PiB uptake among AAs that is at least 13%(15%) higher than in whites. For Aim 1, the study will have 80% power at the 5% significance level to detect correlations of magnitude $|r|=0.20$ (the study from Halder et al[39] showed an R^2 of 11, implying an even greater correlation of 0.33 can be expected in our study). The multivariable regression analysis will have 80% power to detect SWS characteristics that can explain 3% of the variance in the longitudinal change in AD_{PiB}mask (Aim 2) or cognition (Aim 3) after adjusting for covariates that together explain at least 25% of the variance in AD_{PiB}mask/cognition. The detectable effect of 3% variance explained, implies the study can detect partial correlations of magnitude 0.1 between SWS and the outcomes adjusted for the cofactors. It is noted that the power of the multivariable analyses will improve if the covariates explain >25% of the variance. The study will have 80% power to detect sleep measures that explain 10% of the variance in the AD_{PiB}mask ratio even if the covariates explain a negligible percentage of the variance.

9.3 Statistical Methods

General considerations: we will incorporate standard techniques such as omnibus tests and appropriate adjustments to significance (α) levels (*e.g*., Bonferroni correction) for *post-hoc* contrasts to control for multiple comparisons. Both selection and attrition biases might occur. Appropriate techniques (*e.g*., Heckman 2-stage approach (GEE Probit Model)[254;255] and Monte Carlo (EM algorithm)[256] will be used to address biases or missing data. Attributes of those who withdrew to follow-up will be contrasted with completers to determine sources of attrition biases. Since only two time points will be analyzed, we will use linear regression models with the annual rate of amyloid change as dependent variable. Significance will be defined by $p<.05$ where p will be Bonferroni corrected when testing *post-hoc* contrasts.

- **Hypothesis (1):** H1.1) for %AF associations, linear regression models, with each of SWS characteristics as the dependent variable, will be regressed on %AF controlling for age, sex, BMI, AHI, TST, sleep efficiency and WASO. H1.2) This model will test interaction by including the best SWS predictor as dependent variable, the psychosocial factor as a classification factor, %AF and the term created as the cross product of psychosocial factors and %AF.
- **Hypothesis 2-3 (H2-3):** First we will calculate the associations between race and AD_{PiB}mask represented both as binary (AA *vs*. white) and numeric (%AF). Further analyses will use the representation (s) of race significantly associated with amyloid burden. Second, we will use hierarchical

linear regression, with rate of change of AD_{PiB}mask as the dependent variable and race as independent, adjusting for the matching factors: age, sex, BMI, education and annual income (block 1); ApoE4 and ABCA7 (block 2); DWML volumes, DKI indices and mPFC volume (block 3); and SWS characteristic (*e.g.* relative SWA) (block 4). Other covariates (*e.g.,* psychosocial) will be included in the final models if significantly different between AAs and whites as indicated by unequal variance t tests. Although we anticipate that relative SWA will be the best predictor of longitudinal change in AD_{PiB}mask, the best fitting model will be then replicated with each of the other SWS characteristics not listed before. On a final step, we will test whether the effect of SWS on amyloid deposition is different (*i.e.*, stronger) among AAs. The model would include AD_{PiB}mask change, the binary indicator of race (AA=1 *vs*. white=0) and SWA as described in H1.2. If the interaction is significant, it will imply that the effect of SWA on amyloid varies as a function of race. The sign of the estimated coefficient for this term would indicate whether SWA has a significantly stronger or weaker effect among AA. Exploratory Hypothesis: cognitive z-score change in subjects that show improvement in maze CT will be compared with those that don't show improvement using ANCOVA controlling for age, sex, BMI, race, education and ApoE4 status.

- ***Post-hoc* analyses***:* a subset of *post-hoc* analyses will be performed by controlling by PiB levels at baseline and by splitting the sample into PiB+ and PiB- at baseline and performing a separate analysis for each subset. Stratified analyses will also be performed for men and women, as well as for AAs and whites. In addition, we will formally test the impact of PiB status (defined as PiB SUVR≥1.4) on the association of sleep measures with longitudinal increases in AD_{PiB}mask. Although we do not anticipate that sleep or SWS characteristics will change over the follow-up period, *post-hoc* analyses will be performed by assessing longitudinal changes in the sleep measures as correlates and predictors of longitudinal changes in the outcomes measures, using paired sample t-tests to assess the change in outcomes and sleep.

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethics/Protection of Human Subjects

11.1 Ethical Standard

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

11.2 Institutional Review Board

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

11.3 Informed Consent Process

Informed consent is obtained from each subject using IRB approved consent forms. In the consent form and in discussion with an investigator, participants will be advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator (Dr. Osorio). In the informed consent form (ICF), participants will be told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff and the possible exception of state or federal regulatory personnel. Several steps will be taken to minimize reactions of discomfort, embarrassment, fatigue, or boredom.

11.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study procedures, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting procedures. The following consent materials are submitted with this protocol:

- Documentation of Consent Process
- Informed Consent Form
- Screening Form

11.3.2 Consent Procedures and Documentation

Potential study participants will be pre-screened at recruitment sites in a quiet and private area by the study coordinators. A waiver of documentation of consent will be uploaded to the IRB so that people can give verbal consent at the time of the pre-screen. A document with eligibility questions will also be uploaded for approval as a screening form. Given the strict exclusion criteria for this study, a waiver of documentation of consent is necessary in order to avoid wasting participant's time if something makes them clearly ineligible. The pre-screening interview is minimal risk as it involves only the minimum necessary information collected to determine eligibility. This will involve the CES-D, MOSS-F, ARES-TM questionnaire's and review of medical history and medications history. For eligible subjects who subsequently sign consent/authorization to participate, the information becomes part of the subject's de-identified study record. However, information collected during pre-screening will be destroyed immediately if a person is deemed ineligible or decides not to participate in the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will

receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with family members or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of an interpreter, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

11.4 Participant and Data Confidentiality

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

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

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at The Center for Brain Health. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and Center for Brain Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Center for Brain Health.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

This study is a genome-wide association study and will comply with the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted GWAS, which calls for investigators funded by the NIH for GWAS to 1) share de-identified genetic (genotypic and phenotypic) data through a centralized NIH data repository; and 2) submit documentation that describes how the institutions have considered the interests of the research participants, such as privacy and confidentiality. Submission of data to the NIH GWAS repository will be consistent with the permissions and limitations delineated on the study consent signed by study participants.

11.4.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to study the APOE gene. Samples are stored indefinitely. No diagnostic genetic testing will be performed.
- Storage: Access to stored samples over the course of the study will be limited to the PI and co-investigators. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data as well as the linking key to re-identify samples.
- Tracking: Data will be tracked using an Excel tracking file.
    - Disposition at the completion of the study: All stored samples will be sent to the Center for Brain Health (CBH) biorepository. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

Future Use of Stored Specimens:

Subjects will have the option to allow their leftover blood and DNA samples to be banked indefinitely for future research related to studies on early diagnosis of Alzheimer's, disease and/or mechanism of neurodegeneration. After the study is completed, the de-identified, archived data will be transmitted to and stored at the CBH Biorepository, under the supervision of Dr. Osorio, for use by other researchers including those outside of the study. Permission to transmit data to the CBH Biorepository will be included in the ICF. The CBH Biorepository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant which the PI will have access to as well as study team members he gives permission to on a case by case basis. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed. When the study is completed, access to study data and/or samples will be provided through the CBH Biorepository. Samples are stored with the study number, subject ID number, and book period number so they can be withdrawn if necessary.

12 Data Handling and Record Keeping

Data and Safety Monitoring

A data and safety monitoring plan has been established to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the data. Dr. Andrew Varga will conduct data verification and validation of all parameters collected for the study against the source documentation in accordance with the following plan. Periodic discussion every six months between the P.I., Dr. Jean-Louis, and Dr. Varga will ensure a consistent approach to data collection and monitoring techniques for all subjects regarding all relevant information and study procedures such as participant reports, data acquisition

methods, and any safety/adverse events. The primary responsibility of the DSM will be to monitor the progress of the study and recommend modifying the trial or terminating the trial as appropriate.

All studies will be clinically read by a sleep physician from the Icahn School of Medicine at Mount Sinai. These reports will be shared with study subjects. Collected raw data, and processed data exports from the sleep studies will stay in a shared drive based at NYU. Data will be double entered into RedCap by the study coordinators and study interns

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

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

Clinical data and clinical laboratory data will be entered into RedCap, a data capture system provided by the NYU School of Medicine . The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Subject information/data are downloaded into NYU based drives. Mount Sinai teams will log into our drives via the NYU portal with a username and password to process the sleep data and upload the study reports

12.2 Study Records Retention

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

12.3 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NIA Program Official. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

12.4 Publication and Data Sharing Policy

Our plan to share materials and our management of intellectual property will be in accordance with our institution's and NIH policies and guidelines. All investigators involved in this project will adhere to NIH's Data Sharing Policy and Implementation Guidance of March 5, 2003 and NIH Grants Policy on Sharing of

Unique Research Resources including the "Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts" issued in December, 1999. All reasonable requests for additional information or tools developed in-house that are not available from commercial sources will be met in a timely fashion. Our image-analysis software *FireVoxel* can be downloaded at http://wp.nyu.edu/firevoxel/

13 Study Finances

13.1 Funding Source

This grant will be funded by the NIA/NIH

13.2 Costs to the Participant

All study-related costs will be paid by the National Institute of Health (NIH). Participants will not incur any costs as a result of participating in this study.

13.3 Participant Reimbursements or Payments

Participants will receive $150 per NPSG and $200 for the PET-MR scan for a total of $500 for the baseline evaluation and $500 for the 24 fu visit. Subjecs will be compensated with $75 for the 12 month fu visit, totaling $1,075 for entire study completion. Payments are incremental and not contingent upon completing the study.

14 Study Administration

14.1 Study Leadership

Not applicable.

15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the NIH/NIA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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17 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

Attachment A Baseline

Schedule of Events

Activity	Visit 1	Visit 2	Visit 3	Visit 4
Study team procedures				
Informed Consent	X			
Medical History	X			
Physical Exam	X			
Height	X			
Weight	X			
Vitals signs	X			
UDS-3	X			X
Neuropsychological Assessment	X			
3D-Maze			X	
Cardiology assessments				
Electrocardiogram	X			
Laboratory Assessments				
SMA-18	X			
CBC with differential	X			
HbA1c	X			
Imaging Assessments				
PET-MR with PiB				X
Sleep Studies				
Home Sleep Studies	X			
Nocturnal Polysomnography		X	X	X

Attachment A 12 month follow-up

Schedule of Events

Activity	Visit 1	Visit 2	Visit 3	Visit 4
Study team procedures				
Informed Consent	X			
Medical History	X			
Physical Exam	X			
Height	X			
Weight	X			
Vitals signs	X			
UDS-3	X			
Neuropsychological Assessment	X			
3D-Maze				
Cardiology assessments				
Electrocardiogram	X			
Laboratory Assessments				
SMA-18	X			
CBC with differential	X			
HbA1c	X			
Imaging Assessments				
PET-MR with PiB				
Sleep Studies				
Home Sleep Studies				
Nocturnal Polysomnography				

Attachment A Follow-up
Schedule of Events

Activity	Visit 1	Visit 2	Visit 3	Visit 4
Study team procedures				
Informed Consent	X			
Medical History	X			
Physical Exam	X			
Height	X			
Weight	X			
Vitals signs	X			
UDS-3	X			X
Neuropsychological Assessment	X			
3D-Maze			X	
Cardiology assessments				
Electrocardiogram	X			
Laboratory Assessments				
SMA-18	X			
CBC with differential	X			
HbA1c	X			
Imaging Assessments				
PET-MR with PiB				X
Sleep Studies				
Home Sleep Studies	X			
Nocturnal Polysomnography		X	X	X