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Falls: A Marker of Preclinical Alzheimer Disease: A Study Protocol

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Abstract

Introduction: Progression to symptomatic Alzheimer disease occurs slowly over a series of preclinical stages. Declining functional mobility may be an early indicator of loss of brain network integration and may lead to an increased risk of experiencing falls. It is unknown whether measures of functional mobility and falls are preclinical markers of Alzheimer disease. The purpose of this study is to examine: (1) the relationship between falls and functional mobility with Alzheimer disease biomarkers to determine when falls occur within the temporal progression to symptomatic Alzheimer disease, and (2) the attentional compared to perceptual/motor systems that underlie falls and functional mobility changes seen with Alzheimer disease.

Methods and Analysis: This longitudinal cohort study will be conducted at the Knight Alzheimer Disease Research Center. Approximately 350 cognitively normal participants (with and without preclinical Alzheimer disease) will complete an in-home visit every year for 4 years. During each yearly assessment, functional mobility will be assessed using the Performance Oriented Mobility Assessment, Timed Up and Go, and Timed Up and Go dual task. Data regarding falls (including number and severity) will be collected monthly by self-report and confirmed through interviews. This study will leverage ongoing neuropsychological assessments and neuroimaging (including molecular imaging using positron emission tomography and magnetic resonance imaging) performed by the Knight Alzheimer Disease Research Center. Relationships between falls and biomarkers of amyloid, tau, and neurodegeneration will be evaluated.

Ethics and Dissemination: This study was approved by the Washington University in St. Louis Institutional Review Board (reference number 201807135). Written, informed consent will be obtained in the home prior to the collection of any study data. Results will be

published in peer-reviewed publications and presented at national and international conferences.

Keywords: Neurology - Adult neurology, Neurology - Dementia, Neurology - Neurological injury, Neuropathology, Neurophysiology

Trial Registration: ClinicalTrials.gov identifier: N/A

Strengths and Limitations of This Study

- This study is the first to examine whether changes in falls and functional mobility, in conjunction with concurrent brain network changes, can predict progression to Alzheimer disease in older adults.
- This longitudinal study design will enable us to measure falls and functional mobility over 4 years with a well-characterised cohort of 350 community-dwelling older adults who at baseline are cognitively normal (with and without preclinical Alzheimer disease).
- Participants receive a comprehensive in-home evaluation of their fall risks and functional mobility, the results of which are shared with each participant.
- Older adults may not be compliant with fall monitoring over time.
- It may be difficult to differentiate falling from age-related phenotypes such as frailty.

INTRODUCTION

Alzheimer disease (AD) is a slowly progressive neurodegenerative disease that affects 60%–70% of the over 50 million people living with dementia worldwide.[1, 2] Progression to symptomatic AD occurs slowly through a series of preclinical stages marked by changes in molecular biomarkers that can be quantified by neuroimaging, cerebrospinal fluid (CSF), or plasma measures.[3] Cognitively normal (CN) Stage 0 individuals have no biomarker abnormalities. CN Stage 1 individuals have only cerebral amyloidosis, CN Stage 2 individuals have amyloidosis and neurodegeneration, and CN Stage 3 individuals have evidence of amyloidosis, neurodegeneration, and subtle cognitive changes.[4-7] These preclinical stages of AD develop over decades and are considered clinically silent.[3] However, emerging evidence suggests that impaired functional mobility (gait and balance) and subsequent falls[8] may precede symptomatic cognitive impairment.[3, 9] Declining functional mobility and increases in falls may be due to subtle changes in attention, executive, motor, and sensory processing and may be an early indicator of loss of integration between the central (CNS) and peripheral (PNS) nervous systems.[8, 10-12]

Falls are a leading cause of injury, long-term disability, premature institutionalisation, and injury-related death in older individuals.[13, 14] Individuals with symptomatic AD have a 60%–80% increased risk of falling, and those who fall are 5 times more likely to be institutionalised than similar individuals who do not fall.[13, 15] A knowledge gap exists as to whether functional mobility and falls could serve as preclinical markers of AD.[16]

We previously demonstrated that falls occur at higher rates during the preclinical phase of AD, and the mechanisms that underlie the deterioration of cognitive function were associated with declines in gait and balance necessary for functional mobility.[9] Functional connections in

the brain, referred to as resting state functional connectivity (rs-fc), decrease in symptomatic AD.[17] We observed a decrease in rs-fc for CN individuals with preclinical AD in the dorsal attention network (DAN), a set of brain regions involved in attentional control and planning.[17] Functional connections both within the DAN and across other resting state networks may affect one's functional mobility when attempting to navigate home and community environments. While self-reported performance is obtained from CN individuals (with and without preclinical AD), performance-based measures of everyday function are not recorded. Additional research is therefore needed to examine the relationship between functional mobility/falls and rs-fc, especially for CN individuals with preclinical AD.

For this longitudinal observational study, we will evaluate CN individuals (with and without preclinical AD) at baseline who are currently undergoing comprehensive clinical, neuropsychological, and biomarker evaluations at the Knight Alzheimer Disease Research Center (Knight ADRC). Annually, we will conduct an in-home evaluation of fall risks and functional mobility and prospective ascertainment of falls. Comparisons of objective assessments of functional mobility will be performed with regard to measures of brain pathology (using *in vivo* markers of cerebral amyloidosis and neurodegeneration) to allow us to characterise when changes in falls and functional mobility occur during the preclinical stages of AD. We will also examine attentional compared to perceptual/motor systems that underlie falls and functional mobility in preclinical AD. Falls and functional mobility measures could serve as innovative, inexpensive screening tools to identify individuals at increased risk for progression to symptomatic AD. This may have important implications for the timing of interventions in secondary prevention trials in AD and for the development of more precise, effective treatments for individuals with AD.[18]

METHODS AND ANALYSIS

Participants

In this longitudinal cohort study, community-dwelling older adults will be recruited from an existing cohort followed by the Knight ADRC. Inclusion criteria for this study are: ≥65 years of age, CN (Clinical Dementia Rating® (CDR)[19] score of 0, indicating no dementia), and collection of biomarkers (CSF) and/or neuroimaging (positron emission tomography [PET] and/or magnetic resonance imaging [MRI]) within 2 years of study enrolment. Recruitment procedures for the Knight ADRC have been published previously.[20]

Recruitment

Participants (N = 350) will be recruited for in-home visits near the time of their annual clinical assessment at the Knight ADRC. Knight ADRC staff will approach participants who meet inclusion criteria about their interest regarding this study. If interested, potential participants will be referred to a study team member who will provide a detailed description of the study procedures and invite the individual to participate. Letters will also be sent to all eligible individuals to invite them to participate in this study. Written, informed consent will be obtained in the home prior to the collection of any study data. This study was approved by the Institutional Review Board at Washington University in St. Louis (reference number: 201807135).

Study Procedures

All Knight ADRC participants in principle complete longitudinal clinical and neuropsychological assessment and biomarker studies of biofluids (blood, CSF) and

neuroimaging (amyloid PET, structural and functional MRI; see grey boxes in Figure 1). For this study, participants additionally will receive an annual in-home visit and will report falls prospectively for the duration of the study (see blue boxes in Figure 1).

Knight ADRC Clinical Assessment[21]

Knight ADRC participants complete an annual clinical assessment battery administered by an experienced clinician using a standardised protocol. During this visit, the CDR assesses the participant's cognitive and functional performance: 0 = CN, 0.5 = very mild symptomatic AD, 1 = mild symptomatic AD, 2 = moderate symptomatic AD, or 3 = severe symptomatic AD.[19] A neurological examination is performed for each participant. At enrolment, participants must have a CDR = 0.

Knight ADRC Psychometric/Neuropsychological Assessments[22]

Participants complete a standard 2-hour psychometric battery within 2 weeks of their annual clinical assessment by an experienced psychometrist and board-certified neurologist blinded to the participant's preclinical AD status.[22] A sensitive composite of attentional and executive control tests that is highly predictive of the transition from healthy aging to symptomatic AD[23-25] will be compared to functional mobility and fall measures.[22]

Biomarker Acquisition/Brain Neuropathology Assessments[26]

Participants also complete PET scans[27] and MRI[28] and undergo CSF and blood collection[29, 30] at the Knight ADRC every 3 years.

PET imaging

PET imaging will be conducted on a 3T Siemens Biograph mMR hybrid scanner using

the radiotracer [18F] Florbetapir (AV45) to detect *in vivo* presence of amyloid in the brain.[27] Quantitative image analysis will be performed using a standard amyloid imaging analysis protocol[26] that uses FreeSurfer regions of interest (ROIs; Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA). Regional standardised uptake value ratios (SUVRs) will be obtained using the cerebellum as the reference region.

Structural MRI

High-resolution structural MRI scans will be acquired using a T1-weighted magnetisation-prepared rapid gradient echo (MPRAGE) sequence to analyse brain volumetrics. Images will be subsequently analysed using standard procedures developed at the Knight ADRC using FreeSurfer to delineate brain regions,[31] including cortical and subcortical areas, typically affected by AD.[28]

Functional MRI/network dysfunction

During the MRI scan, rs-fc scans will be obtained using a gradient spin-echo sequence. Participants will be instructed to fixate on a visual crosshair and not to fall asleep. Rs-fc pre- and post-processing will be performed using standardised, in-house methods.[32] In preparation for correlation analysis, data will be spatially smoothed with a 6mm full-width at half maximum Gaussian blur. Then, temporal low-pass filtering ($f < 0.1$ Hz) will be applied to the time series of each voxel. Finally, spurious variance will be removed using linear regression for: (1) 6 parameters generated from head motion correction, (2) the whole brain signal, and (3) signals from ventricular and cerebral white matter. An ROI-based analysis consisting of 298 seeds will be performed with a Pearson's correlation coefficient computed between pairwise ROI time courses across all areas within resting state networks (RSNs). From these 298 seeds,

correlation matrices will be generated for each participant. For the 13 RSNs, correlation coefficients across ROI pairs within a network will be averaged to form a composite score. Based on average matrices, both intra-network (diagonal) and inter-network (off diagonal) composite scores will be generated.

CSF biomarkers

CSF will be collected at approximately 8 a.m. following overnight fasting.[33] Twenty to thirty millilitres of CSF are collected, centrifuged briefly at low speed, aliquoted into polypropylene tubes, and then stored at -80˚C. Aβ40, Aβ42, total tau (tTau), and tau phosphorylated at 181 (pTau181) are measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200, Fujirebio[34]) according to the manufacturer's specifications. *APOE* genotype will be determined by genotyping rs7412 and rs429358 using Taqman genotyping technology as described previously.[35]

Preclinical AD staging

Biomarker positivity will be defined by correlating biomarker values at baseline with the risk of developing AD symptoms over time. The derivation of the biomarker cut-offs will be independent of the data collected in this project. Of note, CSF markers of tauopathy (pTau181) and neurodegeneration (tTau) are extremely highly correlated (r ~0.96), so further stratification of stage by tauopathy would not be meaningful.[36] Participants will be classified as: CN if measures of amyloid, neurodegeneration, and episodic memory are normal; Stage 1 if only measures of amyloid are abnormal by CSF Aβ42/Aβ40 or amyloid PET mean cortical SUVRs (which are highly concordant); Stage 2 if only measures of amyloid and neurodegeneration (by CSF tTau) are abnormal; and Stage 3 if measures of amyloid, neurodegeneration, and episodic

memory are abnormal.[37]

Annual In-Home Visit

An occupational therapist (OT), blinded to participants' preclinical AD status, will complete a 120–180-minute in-home visit annually for 4 years. The OT will conduct assessments related to the PNS as well as in-home functional mobility and recognised fall covariates (Tables 1 and 2). Although the annual visit is typically completed in 1 session, it will be completed over 2 sessions if needed due to participant fatigue and/or request. Participants will receive a report with their results from the home visit and fall risk assessment based on established fall risk cut-off scores.[38]

Table 1. Knight ADRC and In-Home Assessments

	Construct	Measure	Description
Central Nervous System	Attentional/ executive control composite derived	Stroop color naming task[51],[a]	Colour naming of congruent (e.g. red), neutral (e.g. deep), or incongruent (e.g. blue) word.
		Simon task[52],[a]	Naming direction of an arrow with a keypress that is spatially consistent or inconsistent with the location of the arrow including congruent and incongruent positioning
		Attentional switching task[53],[a]	Switching every other trial between making odd-even decisions and consonant-vowel decisions on bivalent stimuli (e.g. B14)
Peripheral Nervous System	Standing, balance, and vestibular function	Centre of pressure path[54]	Centre of pressure path will be measured using Balance Tracking System (BTrackS)
	Lower extremity strength and function	30-Second chair stand test[55]	A score below the norm will be considered indicative of decreased lower extremity strength and function
		Handheld dynamometer[56]	Minimal change in the peak torque value for lower extremity strength will be measured
	Grip strength	Handheld dynamometer[57]	Pounds of force will be captured for grip strength
	Vision	Early Treatment Diabetic Retinopathy Study (ETDRS) test[58]	Visual acuity score; number of correct letters read
		Pelli-Robson test[59]	Contrast sensitivity; letter-by-letter
	Sensation	Tuning Fork,[60] Sharp	8-item questionnaire and sensation testing (vibration (feet) and sharp (arms and legs))
Functional Mobility	Dynamic balance and mobility	Performance Oriented Mobility Assessment (POMA)[61]	A task-oriented assessment of 9 balance tasks and 7 items to assess gait
	Gait speed	Timed Up and Go (TUG) test[62]	Timed task of standing up, walking 3m, turning, walking back, and sitting down

	Dual-task gait	Timed Up and Go Cognitive (TUG_{cog})[63]	TUG test while reciting serial 3s with subtractions from various points
	Dual-task gait	Timed Up and Go Manual (TUG_{man})[64]	TUG test while carrying a glass of water
Additional Assessments	Depression	Patient Health Questionnaire (PHQ-9)[65]	10-item questionnaire to assess frequency of symptoms; 0–27 points
		Geriatric Depression Scale-Short Form (GDS-SF)[66][a]	15-item questionnaire; 0–15 points
	Functional performance	Performance Assessment of Self-Care Skills (PASS; Rogers & Holm. Performance Assessment of Self-Care Skills. Unpublished performance test. Pittsburgh, PA: University of Pittsburgh, 1989).	Evaluates independence, safety, and adequacy with shopping, chequebook balancing, and medication management
	Falls behaviour	Falls Behavioral Scale for Older People (FaB)[67]	30-item questionnaire; rated from 1 (least protective) to 4 (most protective) behaviours to prevent falls
	Olfaction	University of Pennsylvania Smell Identification Test (UPSIT)[68]	40-item smell identification test; 0–40 points
	Hearing	Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S)[69]	10-item questionnaire to screen for hearing impairment; 0–40 points
		Brief Hearing Test	Screening tone test at varying frequencies

Note. [a]Collected at the Knight ADRC.

Table 2. Fall Covariate Composite Score Variables

Construct	Measure	Description	Fall risk cut-off[38]
Vision	Early Treatment Diabetic Retinopathy Study (ETDRS) test[58]	Visual acuity score; number of correct letters read	≤12
	Pelli-Robson test[59]	Contrast sensitivity; letter-by-letter	<36 letters
Alcohol abuse	Short Michigan Alcoholism Screening Test – Geriatric Version (SMAST-G)[70]	10-item interview	≥2
Urinary incontinence	Frequency and type[71]	Short questionnaire of frequency and type (stress, urge, or other)	≥weekly urge incontinence
Depression	Geriatric Depression Scale-Short Form (GDS-SF)[66][a]	15-item questionnaire; 0–15 points	>4
Pain	Self-report[72]	Pain scale from 12-item Short Form Survey	≥moderate
Medication	Medication review[a]	Medications and dosages	≥4 medications
Functional capacity	Older Adults Resources and Services Activities of Daily Living (OARS ADL) scale[73]	Ability to perform 14 activities; 0–2 scale, higher scores indicate greater independence	>4
Previous falls	Previous falls[38]	Total falls in past 12 months, self-report	>0
Home hazards	Westmead Home Safety Assessment (WeSHA)[74]	Rates 72 environmental home hazards as hazard/no hazard	≥4 hazards
Self-efficacy	Falls Efficacy Scale – International (FES-ISF)[75]	7 daily activities; rated from 1 (not at all) to 4 (very concerned) about falling during specific activities	>10

Note. [a]Collected at the Knight ADRC.

Monthly Fall Reporting

Participants will report falls prospectively via automated call or e-mail every month for 4 years using the gold-standard for fall reporting, including daily calendar journals, fall interviews, and monetary compensation for reporting.[39] Participants will also receive a standardised fall report form to record the time and location of a fall, nature of the fall environment, specific activity at the time of the fall, and any somatic complaints that proceeded the fall.[40] If a participant reports a fall, an interviewer blinded to preclinical AD status will call the participant

to complete a fall interview to verify the fall, defined as an unintentional movement to the floor, ground, or an object below knee level. The interviewer will then gather additional information about any subsequent injuries or medical treatment.[9, 41, 42] The rate (number) and severity (calculated with a standardised algorithm from medical records and participant report) of falls will be generated.[13] The falls severity score will be quantified using a previously published algorithm: no falls (0), 1 fall without serious injury (1), any fall with minor injury or more than 1 fall (2), and major injury requiring hospitalisation (3).[14]

Measures

An overview of the assessments collected at the Knight ADRC and annual in-home visits, including CNS and PNS measures, functional mobility, additional covariates of interest, and fall covariates, for this study are listed in Tables 1 and 2.

Statistical analysis plan

Data will be entered into Research Electronic Data Capture (REDCap),[43] a secure, web-based application, and analysed using SAS (SAS Institute, Cary, NC, USA). Differences in baseline characteristics across groups will be compared using appropriate statistics (chi-squared test, Student t test, or Mann-Whitney U test). Composites and cut-offs will be calculated as described in the Methods section (see Table 2). Models for analysing AD biomarkers and cognition will include age, gender, fall risk composite score, APOE status (at least APOE ε4 allele), as well as possible interactions among study variables. Models will be implemented using PROC GLM or PROC MIXED/SAS.

Statistical Analysis Plan for the Primary Aim

We will examine the distributions of falls (number and severity) over a 1-year follow-up window and baseline functional mobility scores across the preclinical stages of AD (0, 1, 2, and 3),[4] with appropriate transformations as needed. Falls severity scores across preclinical stages will be compared using analysis of covariance models.[44] Similar analyses will be conducted to compare each of the functional mobility measures across the preclinical stages of AD. We will implement adequate approaches (e.g. Benjamini-Hochberg false discovery procedure[45]) to control for the overall type I error rate due to multiple outcome variables (number and severity of falls, functional mobility) tested in this aim.

We will also jointly model the longitudinal falls severity score and the time-to-symptom onset of AD (defined as the first time a participant receives a CDR > 0) using general linear mixed effects models.[46] For modelling the risk of developing AD, we will use the semiparametric Cox proportional hazards model. To address the association between change in falls and the risk of developing symptomatic AD, we will implement joint models.[47, 48]

Statistical Analysis Plan for the Secondary Aim

We will test a hypothesised model of attentional compared to perceptual/motor systems underlying falls in preclinical AD using structural equation models (SEMs) on cross-sectional data.[49] The structural model will include the estimation of path coefficients among various latent constructs including brain neuropathology, network dysfunction, PNS abnormalities, and falls. We will fit and compare various SEMs for their goodness-of-fit through standard statistics using multiple models.

Sample size calculations

Primary Aim

To examine the relationship between falls, functional mobility, and AD, we will enrol 350 older adults from the Knight ADRC. Based on the distribution of CN participants across clinical stages in the existing Knight ADRC database, the proposed sample size will provide at least 80% statistical power to detect an effect size as small as 0.225 SD on the falls severity score between 2 adjacent participant groups. From the Knight ADRC database, we fitted a survival curve from baseline to the time that a CDR > 0 was first rendered. We found an estimated CDR progression rate of 7.2% per year for individuals with a mean age of 75 at baseline and an expected attrition of approximately 15%. We estimate that approximately 300 participants will be assessed annually throughout the study, and approximately 75 of these individuals will progress to CDR > 0 after baseline. This will provide at least 80% statistical power to detect a 1-fold increase in the risk of developing symptomatic AD for individuals with an increased rate of falls over time compared to those with slow or no changes in falls over time. These power computations were based on a log rank test at the 5% significance level and assumed an annual rate of 4.7% of CDR progression for individuals with slow changes in disability over time.

Secondary Aim

We also tested non-zero path coefficients that link the latent constructs of network dysfunction with attentional compared to perceptual/motor systems, and to impaired functional mobility and falls. The proposed sample provides at least 80% statistical power to detect each path coefficient.

Participants and public involvement

Participants and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Ethics and dissemination

This study was approved by the Washington University in St. Louis Institutional Review Board (reference number 201807135). Written, informed consent will be obtained in the home prior to the collection of any study data. Participants may withdraw from the study at any time. Results will be published in peer-reviewed publications and presented at national and international conferences.

DISCUSSION

Changes in functional mobility and an increase in falls may be an early indicator of preclinical AD.[3, 16, 50] Underlying deviations in functional connectivity may assist in identifying brain RSNs that are affected and lead to falls.[17] Measures of everyday function are not currently included in the evaluation of CN individuals with preclinical AD. To examine these relationships, this study will assess the number and severity of falls, functional mobility (gait and balance), and changes in functional connections (rs-fc) within and across RSNs in a sample of community-dwelling older adults. This will allow us to characterise when changes in falls and functional mobility occur during the preclinical stages of AD as well as potential mechanisms.

The strengths of this study include access to a large, well-characterised cohort of community-dwelling older adults at the Knight ADRC who are enthusiastic about participating in studies. Another strength includes a comprehensive in-home evaluation of a participant's fall risks and functional mobility and the ability to share results with each participant.

Although the strengths are promising, there are a few limitations to this study. First, older adults may not be compliant with fall monitoring over time. The OTs will call

participants to obtain fall information if participants do not want to complete the fall monitoring via automated call or e-mail. Last, it may be difficult to differentiate falling from aging-related phenotypes such as frailty. We will collect information on covariates, including comorbid conditions and other fall risk factors, test these relationships in individuals without preclinical AD, and control for these covariates in statistical analyses.

This study is designed to examine the relationship between falls and functional mobility and underlying attentional compared to perceptual/motor systems in preclinical stages of AD. The findings will enhance our understanding of the systemic manifestations of AD and may identify falls as a previously unknown risk factor for developing preclinical AD. If successful, this study can potentially inform the timing of interventions in secondary prevention trials in AD as well as the development of more precise, effective treatments for individuals at risk for progression to symptomatic AD.[18]

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Author Contributions

The study concept and design was conceived by SLS, BMA, CX, DB, and JM. Patient safety protocols and IRB compliance will be managed by EW, RT, and RB. Recruitment and data collection will be conducted by RMB, RT, and AK. Analysis will be performed by AMF, TB, SES, and CX. The first draft of the protocol was prepared by BA and SS. All authors provided edits and approved the final version of the protocol.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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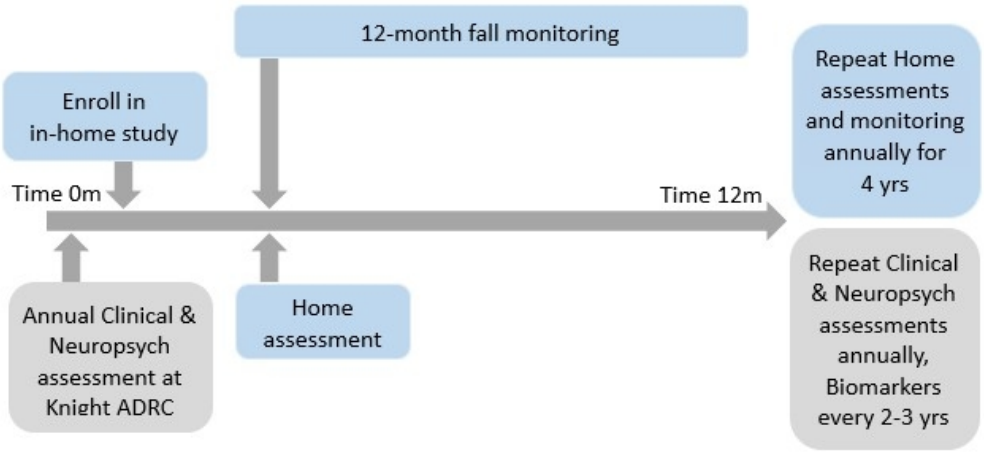
Figure Titles and Legends

Figure 1. Research design overview. Measures of interest collected by the Knight ADRC will be available at no cost. In-home assessments will be collected annually, and falls will be monitored prospectively.



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Falls: A Marker of Preclinical Alzheimer Disease: A Cohort Study Protocol

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Falls: A Marker of Preclinical Alzheimer Disease: A Cohort Study Protocol

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Abstract

Introduction: Progression to symptomatic Alzheimer disease occurs slowly over a series of preclinical stages. Declining functional mobility may be an early indicator of loss of brain network integration and may lead to an increased risk of experiencing falls. It is unknown whether measures of functional mobility and falls are preclinical markers of Alzheimer disease. The purpose of this study is to examine: (1) the relationship between falls and functional mobility with Alzheimer disease biomarkers to determine when falls occur within the temporal progression to symptomatic Alzheimer disease, and (2) the attentional compared to perceptual/motor systems that underlie falls and functional mobility changes seen with Alzheimer disease.

Methods and Analysis: This longitudinal cohort study will be conducted at the Knight Alzheimer Disease Research Center. Approximately 350 cognitively normal participants (with and without preclinical Alzheimer disease) will complete an in-home visit every year for 4 years. During each yearly assessment, functional mobility will be assessed using the Performance Oriented Mobility Assessment, Timed Up and Go, and Timed Up and Go dual task. Data regarding falls (including number and severity) will be collected monthly by self-report and confirmed through interviews. This study will leverage ongoing neuropsychological assessments and neuroimaging (including molecular imaging using positron emission tomography and magnetic resonance imaging) performed by the Knight Alzheimer Disease Research Center. Relationships between falls and biomarkers of amyloid, tau, and neurodegeneration will be evaluated.

Ethics and Dissemination: This study was approved by the Washington University in St. Louis Institutional Review Board (reference number 201807135). Written, informed consent will be obtained in the home prior to the collection of any study data. Results will be

published in peer-reviewed publications and presented at national and international conferences.

Keywords: Neurology - Adult neurology, Neurology - Dementia, Neurology - Neurological injury, Neuropathology, Neurophysiology

Trial Registration: ClinicalTrials.gov identifier: N/A

Strengths and Limitations of This Study

- This study is the first to examine whether changes in falls and functional mobility, in conjunction with concurrent brain network changes, can predict progression to Alzheimer disease in older adults.
- This longitudinal study design will enable us to measure falls and functional mobility over 4 years with a well-characterised cohort of 350 community-dwelling older adults who at baseline are cognitively normal (with and without preclinical Alzheimer disease).
- Participants receive a comprehensive in-home evaluation of their fall risks and functional mobility, the results of which are shared with each participant.
- Older adults may not be compliant with fall monitoring over time.
- It may be difficult to differentiate falling from age-related phenotypes such as frailty.

INTRODUCTION

Alzheimer disease (AD) is a slowly progressive neurodegenerative disease that affects 60%–70% of the over 50 million people living with dementia worldwide.[1, 2] Progression to symptomatic AD occurs slowly through a series of preclinical stages marked by changes in molecular biomarkers that can be quantified by neuroimaging, cerebrospinal fluid (CSF), or plasma measures.[3] Cognitively normal (CN) Stage 0 individuals have no biomarker abnormalities. CN Stage 1 individuals have only cerebral amyloidosis, CN Stage 2 individuals have amyloidosis and neurodegeneration, and CN Stage 3 individuals have evidence of amyloidosis, neurodegeneration, and subtle cognitive changes.[4-7] These preclinical stages of AD develop over decades and are considered clinically silent.[3] However, emerging evidence suggests that impaired functional mobility (gait and balance) and subsequent falls[8] may precede symptomatic cognitive impairment.[3, 9] Declining functional mobility and increases in falls may be due to subtle changes in attention, executive, motor, and sensory processing and may be an early indicator of loss of integration between the central (CNS) and peripheral (PNS) nervous systems.[8, 10-12]

Falls are a leading cause of injury, long-term disability, premature institutionalisation, and injury-related death in older individuals.[13, 14] Individuals with symptomatic AD have a 60%–80% increased risk of falling, and those who fall are 5 times more likely to be institutionalised than similar individuals who do not fall.[13, 15] A knowledge gap exists as to whether functional mobility and falls could serve as preclinical markers of AD.[16]

We previously demonstrated that falls occur at higher rates during the preclinical phase of AD, and the mechanisms that underlie the deterioration of cognitive function were associated with declines in gait and balance necessary for functional mobility.[9] Functional connections in

the brain, referred to as resting state functional connectivity (rs-fc), decrease in symptomatic AD.[17] We observed a decrease in rs-fc for CN individuals with preclinical AD in the dorsal attention network (DAN), a set of brain regions involved in attentional control and planning.[17] Functional connections both within the DAN and across other resting state networks may affect one's functional mobility when attempting to navigate home and community environments. While self-reported performance is obtained from CN individuals (with and without preclinical AD), performance-based measures of everyday function are not recorded. Additional research is therefore needed to examine the relationship between functional mobility/falls and rs-fc, especially for CN individuals with preclinical AD.

For this longitudinal observational study, we will evaluate CN individuals (with and without preclinical AD) at baseline who are currently undergoing comprehensive clinical, neuropsychological, and biomarker evaluations at the Knight Alzheimer Disease Research Center (Knight ADRC). Annually, we will conduct an in-home evaluation of fall risks and functional mobility and prospective ascertainment of falls. Comparisons of objective assessments of functional mobility will be performed with regard to measures of brain pathology (using *in vivo* markers of cerebral amyloidosis and neurodegeneration) to allow us to characterise when changes in falls and functional mobility occur during the preclinical stages of AD. We will also examine attentional compared to perceptual/motor systems that underlie falls and functional mobility in preclinical AD. Falls and functional mobility measures could serve as innovative, inexpensive screening tools to identify individuals at increased risk for progression to symptomatic AD. This may have important implications for the timing of interventions in secondary prevention trials in AD and for the development of more precise, effective treatments for individuals with AD.[18]

METHODS AND ANALYSIS

Participants

In this longitudinal cohort study, community-dwelling older adults will be recruited from an existing cohort followed by the Knight ADRC. Inclusion criteria for this study are: ≥65 years of age, CN (Clinical Dementia Rating® (CDR)[19] score of 0, indicating no dementia), and collection of biomarkers (CSF) and/or neuroimaging (positron emission tomography [PET] and/or magnetic resonance imaging [MRI]) within 2 years of study enrolment. Recruitment procedures for the Knight ADRC have been published previously.[20]

Recruitment

Participants (N = 350) will be recruited for in-home visits near the time of their annual clinical assessment at the Knight ADRC. Knight ADRC staff will approach participants who meet inclusion criteria about their interest regarding this study. If interested, potential participants will be referred to a study team member who will provide a detailed description of the study procedures and invite the individual to participate. Letters will also be sent to all eligible individuals to invite them to participate in this study. Written, informed consent will be obtained in the home prior to the collection of any study data. This study was approved by the Institutional Review Board at Washington University in St. Louis (reference number: 201807135).

Study Procedures

All Knight ADRC participants in principle complete longitudinal clinical and neuropsychological assessment and biomarker studies of biofluids (blood, CSF) and

neuroimaging (amyloid PET, structural and functional MRI; see grey boxes in Figure 1). For this study, participants additionally will receive an annual in-home visit and will report falls prospectively for the duration of the study (see blue boxes in Figure 1).

Knight ADRC Clinical Assessment[21]

Knight ADRC participants complete an annual clinical assessment battery administered by an experienced clinician using a standardised protocol. During this visit, the CDR assesses the participant's cognitive and functional performance: 0 = CN, 0.5 = very mild symptomatic AD, 1 = mild symptomatic AD, 2 = moderate symptomatic AD, or 3 = severe symptomatic AD.[19] A neurological examination is performed for each participant. At enrolment, participants must have a CDR = 0.

Knight ADRC Psychometric/Neuropsychological Assessments[22]

Participants complete a standard 2-hour psychometric battery within 2 weeks of their annual clinical assessment by an experienced psychometrist and board-certified neurologist blinded to the participant's preclinical AD status.[22] A sensitive composite of attentional and executive control tests that is highly predictive of the transition from healthy aging to symptomatic AD[23-25] will be compared to functional mobility and fall measures.[22]

Biomarker Acquisition/Brain Neuropathology Assessments[26]

Participants also complete PET scans[27] and MRI[28] and undergo CSF and blood collection[29, 30] at the Knight ADRC every 3 years.

PET imaging

PET imaging will be conducted on a 3T Siemens Biograph mMR hybrid scanner using

the radiotracer [18F] Florbetapir (AV45) to detect *in vivo* presence of amyloid in the brain.[27] Quantitative image analysis will be performed using a standard amyloid imaging analysis protocol[26] that uses FreeSurfer regions of interest (ROIs; Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA). Regional standardised uptake value ratios (SUVRs) will be obtained using the cerebellum as the reference region.

Structural MRI

High-resolution structural MRI scans will be acquired using a T1-weighted magnetisation-prepared rapid gradient echo (MPRAGE) sequence to analyse brain volumetrics. Images will be subsequently analysed using standard procedures developed at the Knight ADRC using FreeSurfer to delineate brain regions,[31] including cortical and subcortical areas, typically affected by AD.[28]

Functional MRI/network dysfunction

During the MRI scan, rs-fc scans will be obtained using a gradient spin-echo sequence. Participants will be instructed to fixate on a visual crosshair and not to fall asleep. Rs-fc pre- and post-processing will be performed using standardised, in-house methods.[32] In preparation for correlation analysis, data will be spatially smoothed with a 6mm full-width at half maximum Gaussian blur. Then, temporal low-pass filtering ($f < 0.1$ Hz) will be applied to the time series of each voxel. Finally, spurious variance will be removed using linear regression for: (1) 6 parameters generated from head motion correction, (2) the whole brain signal, and (3) signals from ventricular and cerebral white matter. An ROI-based analysis consisting of 298 seeds will be performed with a Pearson's correlation coefficient computed between pairwise ROI time courses across all areas within resting state networks (RSNs). From these 298 seeds,

correlation matrices will be generated for each participant. For the 13 RSNs, correlation coefficients across ROI pairs within a network will be averaged to form a composite score. Based on average matrices, both intra-network (diagonal) and inter-network (off diagonal) composite scores will be generated.

CSF biomarkers

CSF will be collected at approximately 8 a.m. following overnight fasting.[33] Twenty to thirty millilitres of CSF are collected, centrifuged briefly at low speed, aliquoted into polypropylene tubes, and then stored at -80˚C. Aβ40, Aβ42, total tau (tTau), and tau phosphorylated at 181 (pTau181) are measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200, Fujirebio)[34] according to the manufacturer's specifications. *APOE* genotype will be determined by genotyping rs7412 and rs429358 using Taqman genotyping technology as described previously.[35]

Preclinical AD staging

Biomarker positivity will be defined by correlating biomarker values at baseline with the risk of developing AD symptoms over time. The derivation of the biomarker cut-offs will be independent of the data collected in this project. Of note, CSF markers of tauopathy (pTau181) and neurodegeneration (tTau) are extremely highly correlated (r ~0.96), so further stratification of stage by tauopathy would not be meaningful.[36] Participants will be classified as: CN if measures of amyloid, neurodegeneration, and episodic memory are normal; Stage 1 if only measures of amyloid are abnormal by CSF Aβ42/Aβ40 or amyloid PET mean cortical SUVRs (which are highly concordant); Stage 2 if only measures of amyloid and neurodegeneration (by CSF tTau) are abnormal; and Stage 3 if measures of amyloid, neurodegeneration, and episodic

memory are abnormal.[37]

Annual In-Home Visit

An occupational therapist (OT), blinded to participants' preclinical AD status, will complete a 120–180-minute in-home visit annually for 4 years. The OT will conduct assessments related to the PNS as well as in-home functional mobility and recognised fall covariates (Tables 1 and 2). Although the annual visit is typically completed in 1 session, it will be completed over 2 sessions if needed due to participant fatigue and/or request. Participants will receive a report with their results from the home visit and fall risk assessment based on established fall risk cut-off scores.[38]

Table 1. Knight ADRC and In-Home Assessments

	Construct	Measure	Description
Central Nervous System	Attentional/ executive control composite derived	Stroop color naming task[39][a]	Colour naming of congruent (e.g. red), neutral (e.g. deep), or incongruent (e.g. blue) word.
		Simon task[40][a]	Naming direction of an arrow with a keypress that is spatially consistent or inconsistent with the location of the arrow including congruent and incongruent positioning
		Attentional switching task[41][a]	Switching every other trial between making odd-even decisions and consonant-vowel decisions on bivalent stimuli (e.g. B14)
Peripheral Nervous System	Standing, balance, and vestibular function	Centre of pressure path[42]	Centre of pressure path will be measured using Balance Tracking System (BTrackS)
	Lower extremity strength and function	30-Second chair stand test[43]	A score below the norm will be considered indicative of decreased lower extremity strength and function
		Handheld dynamometer[44]	Minimal change in the peak torque value for lower extremity strength will be measured
	Grip strength	Handheld dynamometer[45]	Pounds of force will be captured for grip strength
	Vision	Early Treatment Diabetic Retinopathy Study (ETDRS) test[46]	Visual acuity score; number of correct letters read
		Pelli-Robson test[47]	Contrast sensitivity; letter-by-letter
	Sensation	Tuning Fork, Sharp[48]	8-item questionnaire and sensation testing (vibration (feet) and sharp (arms and legs))
Functional Mobility	Dynamic balance and mobility	Performance Oriented Mobility Assessment (POMA)[49]	A task-oriented assessment of 9 balance tasks and 7 items to assess gait
	Gait speed	Timed Up and Go (TUG) test[50]	Timed task of standing up, walking 3m, turning, walking back, and sitting down
	Dual-task gait	Timed Up and Go Cognitive (TUG_{cog})[51]	TUG test while reciting serial 3s with subtractions from various points

Table 2. Fall Covariate Composite Score Variables

	Construct	Measure	Description	Fall risk cut-off[38]
	Vision	Early Treatment Diabetic Retinopathy Study (ETDRS) test[46]	Visual acuity score; number of correct letters read	≤12
		Pelli-Robson test[47]	Contrast sensitivity; letter-by-letter	<36 letters
	Alcohol abuse	Short Michigan Alcoholism Screening Test – Geriatric Version (SMAST-G)[53]	10-item interview	≥2
	Depression	Geriatric Depression Scale-Short Form (GDS-SF)[55][a]	15-item questionnaire; 0–15 points	>4
	Urinary incontinence	Frequency and type[56]	Short questionnaire of frequency and type (stress, urge, or other)	≥weekly urge incontinence
	Pain	Self-report[57]	Pain scale from 12-item Short Form Survey	≥moderate
	Medication	Medication review[a]	Medications and dosages	≥4 medications
	Functional capacity	Older Adults Resources and Services Activities of Daily Living (OARS	Ability to perform 14 activities; 0–2 scale, higher scores indicate greater	>4
	Dual-task gait	Timed Up and Go Manual (TUG_{man})[52]	TUG test while carrying a glass of water	
Additional Assessments	Alcohol abuse	Short Michigan Alcoholism Screening Test – Geriatric Version (SMAST-G)[53]	10-item interview	
	Depression	Patient Health Questionnaire (PHQ-9)[54]	10-item questionnaire to assess frequency of symptoms; 0–27 points	
		Geriatric Depression Scale-Short Form (GDS-SF)[55][a]	15-item questionnaire; 0–15 points	
	Urinary incontinence	Frequency and type[56]	Short questionnaire of frequency and type (stress, urge, or other)	
	Pain	Self-report[57]	Pain scale from 12-item Short Form Survey	
	Medication	Medication review[a]	Medications and dosages	
	Functional capacity	Older Adults Resources and Services Activities of Daily Living (OARS ADL) scale[58]	Ability to perform 14 activities; 0–2 scale, higher scores indicate greater independence	
	Functional performance	Performance Assessment of Self-Care Skills (PASS)[59]	Evaluates independence, safety, and adequacy with shopping, chequebook balancing, and medication management	
	Falls behaviour	Falls Behavioral Scale for Older People (FaB)[60]	30-item questionnaire; rated from 1 (least protective) to 4 (most protective) behaviours to prevent falls	
	Self-efficacy	Falls Efficacy Scale – International (FES-ISF)[61]	7 daily activities; rated from 1 (not at all) to 4 (very concerned) about falling during specific activities	
	Home hazards	Westmead Home Safety Assessment (WeSHA)[62]	Rates 72 environmental home hazards as hazard/no hazard	
	Olfaction	University of Pennsylvania Smell Identification Test (UPSIT)[63]	40-item smell identification test; 0–40 points	
	Hearing	Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S)[64]	10-item questionnaire to screen for hearing impairment; 0–40 points	
		Brief Hearing Test	Screening tone test at varying frequencies	

Note. [a]Collected at the Knight ADRC.

	ADL) scale[58]	independence	
Previous falls	Previous falls[38]	Total falls in past 12 months, self-report	>0
Home hazards	Westmead Home Safety Assessment (WeSHA)[62]	Rates 72 environmental home hazards as hazard/no hazard	≥4 hazards
Self-efficacy	Falls Efficacy Scale – International (FES-ISF)[61]	7 daily activities; rated from 1 (not at all) to 4 (very concerned) about falling during specific activities	>10

Note. [a]Collected at the Knight ADRC.

Monthly Fall Reporting

Participants will report falls prospectively via automated call or e-mail every month for 4 years using the gold-standard for fall reporting, including daily calendar journals, fall interviews, and monetary compensation for reporting.[65] Participants will also receive a standardised fall report form to record the time and location of a fall, nature of the fall environment, specific activity at the time of the fall, and any somatic complaints that proceeded the fall.[66] If a participant reports a fall, an interviewer blinded to preclinical AD status will call the participant to complete a fall interview to verify the fall, defined as an unintentional movement to the floor, ground, or an object below knee level. The interviewer will then gather additional information about any subsequent injuries or medical treatment.[9, 67, 68] The rate (number) and severity (calculated with a standardised algorithm from medical records and participant report) of falls will be generated.[13] The falls severity score will be quantified using a previously published algorithm: no falls (0), 1 fall without serious injury (1), any fall with minor injury or more than 1 fall (2), and major injury requiring hospitalisation (3).[14]

Measures

An overview of the assessments collected at the Knight ADRC and annual in-home visits, including CNS and PNS measures, functional mobility, additional covariates of interest, and fall covariates, for this study are listed in Tables 1 and 2.

Statistical analysis plan

Data will be entered into Research Electronic Data Capture (REDCap),[69] a secure, web-based application, and analysed using SAS (SAS Institute, Cary, NC, USA). Differences in baseline characteristics across groups will be compared using appropriate statistics (chi-squared test, Student t test, or Mann-Whitney U test). Composites and cut-offs will be calculated as described in the Methods section (see Table 2). Models for analysing AD biomarkers and cognition will include age, gender, fall risk composite score, APOE status (at least APOE ε4 allele), as well as possible interactions among study variables. Models will be implemented using PROC GLM or PROC MIXED/SAS.

Statistical Analysis Plan for the Primary Aim

We will examine the distributions of falls (number and severity) over a 1-year follow-up window and baseline functional mobility scores across the preclinical stages of AD (0, 1, 2, and 3),[4] with appropriate transformations as needed. Falls severity scores across preclinical stages will be compared using analysis of covariance models.[70] Similar analyses will be conducted to compare each of the functional mobility measures across the preclinical stages of AD. We will implement adequate approaches (e.g. Benjamini-Hochberg false discovery procedure)[71] to control for the overall type I error rate due to multiple outcome variables (number and severity of falls, functional mobility) tested in this aim.

We will also jointly model the longitudinal falls severity score and the time-to-symptom onset of AD (defined as the first time a participant receives a CDR > 0) using general linear mixed effects models.[72] For modelling the risk of developing AD, we will use the semiparametric Cox proportional hazards model. To address the association between change in falls and the risk of developing symptomatic AD, we will implement joint models.[73, 74]

Statistical Analysis Plan for the Secondary Aim

We will test a hypothesised model of attentional compared to perceptual/motor systems underlying falls in preclinical AD using structural equation models (SEMs) on cross-sectional data.[75] The structural model will include the estimation of path coefficients among various latent constructs including brain neuropathology, network dysfunction, PNS abnormalities, and falls. We will fit and compare various SEMs for their goodness-of-fit through standard statistics using multiple models.

Sample size calculations

Primary Aim

To examine the relationship between falls, functional mobility, and AD, we will enrol 350 older adults from the Knight ADRC. Based on the distribution of CN participants across clinical stages in the existing Knight ADRC database, the proposed sample size will provide at least 80% statistical power to detect an effect size as small as 0.225 SD on the falls severity score between 2 adjacent participant groups. From the Knight ADRC database, we fitted a survival curve from baseline to the time that a CDR > 0 was first rendered. We found an estimated CDR progression rate of 7.2% per year for individuals with a mean age of 75 at baseline and an expected attrition of approximately 15%. We estimate that approximately 300 participants will be assessed annually throughout the study, and approximately 75 of these individuals will progress to CDR > 0 after baseline. This will provide at least 80% statistical power to detect a 1-fold increase in the risk of developing symptomatic AD for individuals with an increased rate of falls over time compared to those with slow or no changes in falls over time. These power

computations were based on a log rank test at the 5% significance level and assumed an annual rate of 4.7% of CDR progression for individuals with slow changes in disability over time.

Secondary Aim

We also tested non-zero path coefficients that link the latent constructs of network dysfunction with attentional compared to perceptual/motor systems, and to impaired functional mobility and falls. The proposed sample provides at least 80% statistical power to detect each path coefficient.

Participants and public involvement

Participants and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Ethics and dissemination

This study was approved by the Washington University in St. Louis Institutional Review Board (reference number 201807135). Written, informed consent will be obtained in the home prior to the collection of any study data. Participants may withdraw from the study at any time. Results will be published in peer-reviewed publications and presented at national and international conferences.

DISCUSSION

Changes in functional mobility and an increase in falls may be an early indicator of preclinical AD.[3, 16, 76] Underlying deviations in functional connectivity may assist in identifying brain RSNs that are affected and lead to falls.[17] Measures of everyday function are not currently included in the evaluation of CN individuals with preclinical AD. To

examine these relationships, this study will assess the number and severity of falls, functional mobility (gait and balance), and changes in functional connections (rs-fc) within and across RSNs in a sample of community-dwelling older adults. This will allow us to characterise when changes in falls and functional mobility occur during the preclinical stages of AD as well as potential mechanisms.

The strengths of this study include access to a large, well-characterised cohort of community-dwelling older adults at the Knight ADRC who are enthusiastic about participating in studies. Another strength includes a comprehensive in-home evaluation of a participant's fall risks and functional mobility and the ability to share results with each participant.

Although the strengths are promising, there are a few limitations to this study. First, older adults may not be compliant with fall monitoring over time. The OTs will call participants to obtain fall information if participants do not want to complete the fall monitoring via automated call or e-mail. Last, it may be difficult to differentiate falling from aging-related phenotypes such as frailty. We will collect information on covariates, including comorbid conditions and other fall risk factors, test these relationships in individuals without preclinical AD, and control for these covariates in statistical analyses.

This study is designed to examine the relationship between falls and functional mobility and underlying attentional compared to perceptual/motor systems in preclinical stages of AD. The findings will enhance our understanding of the systemic manifestations of AD and may identify falls as a previously unknown risk factor for developing preclinical AD. If successful, this study can potentially inform the timing of interventions in secondary prevention trials in AD as well as the development of more precise, effective treatments for individuals at risk for progression to symptomatic AD.[18]

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Author Contributions

The study concept and design was conceived by SLS, BMA, CX, DB, and JM. Patient safety protocols and IRB compliance will be managed by EW, RT, and RB. Recruitment and data collection will be conducted by RMB, RT, and AK. Analysis will be performed by AMF, TB, SES, and CX. The first draft of the protocol was prepared by BMA and SLS. All authors provided edits and approved the final version of the protocol.

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Competing interests

There are no competing interests for any author.

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Figure Titles and Legends

Figure 1. Research design overview. Measures of interest collected by the Knight ADRC will be available at no cost. In-home assessments will be collected annually, and falls will be monitored prospectively.

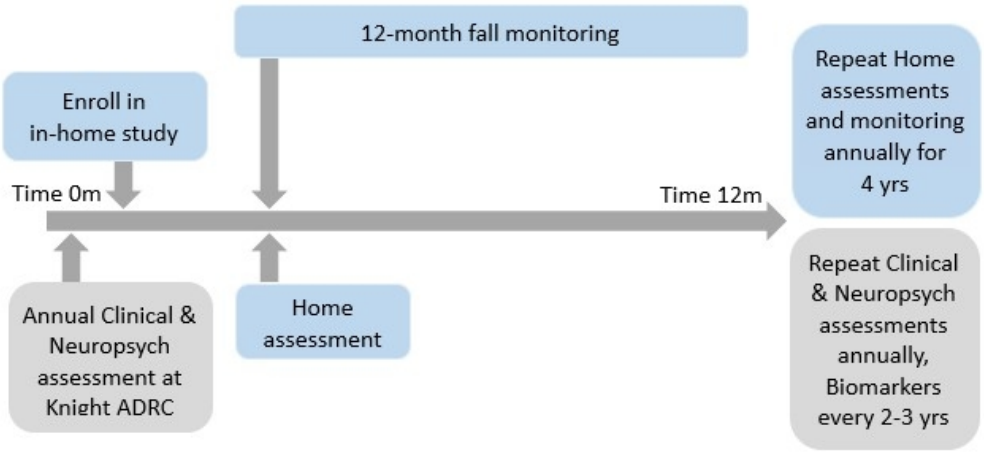

Figure 1. Research design overview. Measures of interest collected by the Knight ADRC will be available at no cost. In-home assessments will be collected annually, and falls will be monitored prospectively.

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