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RESEARCH ARTICLE

The U.S. POINTER neurovascular ancillary study: Study design and methods

Tina E. Brinkley[1] | Katelyn R. Garcia[2] | Gary F. Mitchell[3] | Charles H. Tegeler[4] | Aarti Sarwal[4] | John Bennett[4] | Dalane W. Kitzman[1,5] | Iris Leng[2] | Laura D. Baker[1,6] | Mark A. Espeland[1] | Heather M. Snyder[7] | Jurgen A. Claassen[8] | Margie J. Bailey[9] | Hossam A. Shaltout[9,10]

[1]Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[2]Department of Biostatistics and Data Science, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[3]Cardiovascular Engineering Inc., Norwood, Massachusetts, USA

[4]Department of Neurology, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, North Carolina, USA

[5]Department of Internal Medicine, Section on Cardiovascular Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[6]Department of Social Sciences and Health Policy, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[7]Division of Medical and Scientific Relations, Alzheimer's Association, Chicago, Illinois, USA

[8]Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands

[9]Hypertension and Vascular Research Center, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[10]Department of Obstetrics and Gynecology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Correspondence
Tina Brinkley, Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA.
Email: tbrinkle@wakehealth.edu

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Abstract

INTRODUCTION: POINTER Neurovascular (POINTER-NV) is an ancillary study that leverages the rich infrastructure and design of the U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) to investigate neurovascular mechanisms that may underlie intervention effects on key brain outcomes.

METHODS: A comprehensive neurovascular assessment is conducted at baseline, Month 12, and Month 24 using a variety of complementary non-invasive techniques including transcranial Doppler ultrasound, carotid ultrasound, echocardiography, tonometry, and continuous blood pressure and heart rate monitoring. Measurements are acquired at rest and during orthostatic challenges, hyperventilation, and carbon dioxide inhalation.

RESULTS: The primary outcomes are baroreflex sensitivity and cerebral autoregulation. Secondary outcomes include aortic, carotid, and cerebral hemodynamics and various measures of autonomic function and vascular structure and function.

DISCUSSION: POINTER-NV will provide critical insight into neurovascular mechanisms that may change with intensive lifestyle modification and promote improvements in cognition and overall brain health.

KEYWORDS
aging, arterial stiffness, autonomic function, cerebral autoregulation, clinical trial, dementia, lifestyle intervention, prevention, vascular function

Highlights

- This study takes advantage of U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) to address key gaps in the field.
- POINTER Neurovascular (POINTER-NV) will provide insight into neurovascular mechanisms underlying dementia.
- POINTER-NV may help shed light on modifiable vascular contributions to dementia.

1 | BACKGROUND

Alzheimer's disease (AD) has traditionally been defined using biomarkers of amyloid, tau, and neurodegeneration, which fails to account for the fact that the clinical syndrome is marked by significant heterogeneity and mixed pathologies.[1,2] In fact, vascular contributions to cognitive impairment and dementia likely play a major role in the pathophysiology of AD and related dementias (ADRD). Vascular risk factors such as hypertension, diabetes, and hypercholesterolemia may contribute to or modify the onset and progression of clinical symptoms, in part by inducing cerebrovascular injury and lowering the threshold for neuronal dysfunction and loss.[3] These risk factors are also associated with chronic cerebral hypoperfusion, which precedes and contributes to the development of cognitive impairment and ADRD.[4,5] Thus, quantifying vascular biomarkers in ADRD research may help to better capture pathophysiological changes underlying cognitive decline and dementia.[2]

Studies show that up to one third of ADRD cases are associated with modifiable vascular risk factors, including obesity, diabetes, and hypertension.[6–8] As such, interventions that target vascular risk factors, especially those that present early in the disease pathway, may have the potential to delay or prevent the development of ADRD. Growing evidence highlights the role of non-pharmacological approaches in promoting brain health and the maintenance of cognitive function with advancing age. However, more studies are needed, particularly randomized clinical trials that shed light on the vascular contributions to ADRD and their joint trajectories with neuropathological and cognitive changes over time. In 2015 the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) published exciting results indicating that a multidomain lifestyle intervention can help older adults at risk for cognitive decline to maintain or improve their cognitive trajectory.[9] Three years later the U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) was launched to investigate the generalizability of the FINGER findings in a geographically and racially diverse cohort of Americans who are cognitively normal but at risk for cognitive decline and dementia due to well-established risk factors.[10] U.S. POINTER was specifically designed to test whether random assignment to one of two lifestyle interventions alters cognitive trajectory over 2 years in 2000 older adults aged 60 to 79 years using a similar multimodal intervention approach as the FINGER study.

Given the importance of vascular risk factors and the dearth of information regarding connections between the central nervous system and the local and systemic vasculature within the context of a lifestyle intervention, a neurovascular ancillary study to U.S. POINTER was developed to fill important gaps in the field. POINTER Neurovascular (POINTER-NV) leverages the rich resources of the main trial to expand the scope and impact of this research and help us further understand potential mechanisms through which a multimodal lifestyle intervention might alter the trajectory of cognitive decline in at-risk older adults. Here we describe the rationale, study design, and methods used in the POINTER-NV ancillary study to assess multiple measures of neurovascular health.

2 | METHODS

2.1 | Study rationale

Adequate cerebral blood flow is necessary to maintain a constant supply of oxygen and nutrients to the metabolically active brain. While the relevance of reduced cerebral blood flow in ADRD is well documented,[11,12] very few studies have investigated the role of upstream regulators of cerebral blood flow in the context of ADRD or long-term lifestyle interventions. Age-related dysfunction of homeostatic mechanisms involved in the dynamic regulation of cerebral blood flow plays an important role in the pathophysiology of brain aging and likely renders the aging brain more susceptible to the damaging effects of comorbid conditions, such as hypertension, diabetes, and hypercholesterolemia. Cerebral autoregulation and baroreflex sensi-

tivity are two key mechanisms that regulate cerebral blood flow at the local and systemic level, respectively, through an integrative process that is modulated by age-related changes in vascular structure and function.[13] Impairments in these neurovascular mechanisms may promote repeated transient episodes of cerebral hypoperfusion, thereby promoting progressive parenchymal damage, cognitive decline, and ADRD.[11,13] Several short-term intervention studies show positive effects of regular aerobic exercise and a healthy diet on baroreflex sensitivity.[13–16] While cross-sectional studies suggest cerebral autoregulation is largely unchanged in trained athletes,[13,17] there is a paucity of data on cerebral autoregulation after exercise training or other lifestyle interventions. Moreover, whether intervention-related changes in neurovascular mechanisms correlate with improvements in cognition and overall brain heath remains unclear. As such, taking advantage of the multidomain lifestyle intervention in U.S. POINTER allows for a robust investigation into neural and vascular pathways that can impact the brain, which may provide insight into early biomarkers of disease and their modification by healthy lifestyle changes.

The arterial baroreflex maintains stable perfusion pressure across the cerebrovascular bed via vagal and sympathetic control of heart rate, myocardial contractility, and total peripheral resistance,[18] while cerebral autoregulation operates at the level of the end-organ to stabilize cerebral blood flow against dynamic changes in blood pressure by modulating cerebrovascular resistance through myogenic, metabolic, and neurogenic mechanisms.[19] If either of these control systems fail, cerebral blood flow can be compromised. Thus, the focus on baroreflex sensitivity and cerebral autoregulation as primary neurovascular outcomes highlights the importance of these integrated measures that reflect neural pathways as well as structural and functional characteristics of the vasculature. Including specific measures of vascular structure and function (e.g., arterial stiffness, carotid intima-media thickness [IMT]) as secondary outcomes helps to further refine the vascular characteristics that can modulate the regulatory pathways of interest and ultimately influence blood flow to the brain. Importantly, these secondary outcomes are also known to improve with lifestyle changes and may parallel improvements in brain health.[13,15,20–22]

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed using standard sources (e.g., PubMed). Prior studies on similar multimodal lifestyle interventions and neurovascular outcomes have been reported and are referenced in the article.
2. **Interpretation**: This article describes the rationale, study design, and methods for an ancillary study to the largest lifestyle intervention trial in the United States to date that focuses on brain health and risk for Alzheimer's disease and related dementias. This study will be the first of its kind, providing critical insight into neurovascular mechanisms that may underlie lifestyle-induced changes in cognitive function and overall brain health.
3. **Future directions**: The results of this study could identify key neurovascular pathways that can be targeted with lifestyle or pharmacological approaches to alter the trajectory of cognitive decline and dementia.

2.2 | Study overview

POINTER-NV aims to provide critical insight into key neurovascular mechanisms that may underlie healthy lifestyle effects on cognitive function in U.S. POINTER participants. POINTER-NV adds measurements of aortic, carotid, and cerebral hemodynamics using complementary non-invasive techniques including ultrasound, tonometry, echocardiography, and continuous blood pressure and heart rate monitoring at rest, during orthostatic challenges, hyperventilation, and carbon dioxide (CO_2) inhalation. These measurements allow for a comprehensive assessment of autonomic function, cerebral autoregulation, and vascular structure and function. The primary, secondary, and exploratory outcomes are described below and listed in Table 1. POINTER-NV also aims to investigate whether intervention-related improvements in neurovascular outcomes correlate with 2-year improvements in cognition and brain structure and function. The overall hypothesis is that the U.S. POINTER multimodal lifestyle intervention will improve cerebral autoregulation, baroreflex sensitivity, autonomic function, and vascular structure and function and that greater improvements in these neurovascular outcomes will be associated with more favorable changes in brain health. We anticipate that the primary neurovascular outcomes (baroreflex sensitivity, cerebral autoregulation) will have both direct and indirect associations with cognition, with indirect effects being mediated in part by brain structure and function. We anticipate similar results for the secondary neurovascular outcomes, although some of them (e.g., aortic stiffness) may also directly influence the primary outcomes. Given the complex and multifaceted interactions between the outcomes of interest, determining how the different neurovascular measures work together (e.g., as independent or overlapping factors) to impact brain health will be a key priority of the POINTER-NV ancillary study.

2.3 | Study organization

POINTER-NV takes advantage of the study design and existing infrastructure of the main trial, which has been described previously.[10] In brief, participants are recruited from five clinical sites across the United States that bring geographic, racial, and ethnic diversity: Wake Forest University School of Medicine in North Carolina, University of California Davis in Northern California, Rush University Medical Center and Advocate Health in Illinois, Baylor College of Medicine and Kelsey Research Foundation in Texas, and Brown University/Butler Hospital in Rhode Island. Eligible participants are randomly assigned to one of two lifestyle interventions that differ in intensity, accountability, and format. Participants assigned to the self-guided intervention arm attend

TABLE 1 Key POINTER-NV outcomes of interest.

Primary outcomes	Method	Position(s)	Key metric (units)
Baroreflex sensitivity	Continuous BP and ECG	standing and seated	Sequence ALL (ms/mmHg)
Cerebral autoregulation	Transcranial Doppler	standing and seated	Gain (cm/s/mmHg) and phase (degrees)
Secondary outcomes	**Method**	**Position(s)**	**Key metric (units)**
Aortic stiffness	Tonometry and ECG	Supine	Carotid-femoral PWV (m/s)
Carotid stiffness	Vascular ultrasound	Supine	Carotid distensibility ($1/kPa \times 10^{-3}$)
Subclinical atherosclerosis	Vascular ultrasound	Supine	Carotid IMT (mm)
Cerebrovascular function	Transcranial Doppler	Seated	Cerebral vasomotor reactivity (%/mmHg)
Heart rate variability	Continuous ECG	Supine, standing, seated	SDNN and rMSSD (ms)
Orthostatic hypotension	Continuous BP	Supine to standing	Change in BP (mmHg)
Central BP	Tonometry	Supine	Aortic and carotid BP (mmHg)
Aortic flow	Echocardiography	Supine	Aortic flow velocities (cm/s) and pulsatility index
Carotid flow	Vascular ultrasound	Supine	Carotid flow velocities (cm/s) and pulsatility index
Cerebral flow	Transcranial Doppler	Seated	Cerebral flow velocities (cm/s) and pulsatility index

Abbreviations: BP, blood pressure; ECG, electrocardiography; IMT, intima-media thickness, PWV, pulse wave velocity, rMSSD, root mean square of successive differences; POINTER-NV, Protect Brain Health through Lifestyle Intervention to Reduce Risk–Neurovascular; SDNN, standard deviation of *N* to *N* intervals.

facilitated group meetings two to three times per year for education and support. Participants assigned to the structured intervention arm complete a more intensive program that includes structured physical and cognitive exercise programs, nutritional counseling to encourage adherence to the MIND diet (a hybrid of the Mediterranean and Dietary Approaches to Stop Hypertension [DASH] diets), and health coaching for cardiometabolic risk management. Participants in both groups receive annual results from clinical laboratory blood tests and vital signs assessments. Clinic visits for the main trial are conducted at baseline and at 6-month intervals through Month 24 to assess cognitive, laboratory, functional, and other health-related outcomes.

Central oversight of the trial's clinical operations, intervention delivery, outcomes assessment, participant safety, and data management are provided by the U.S. POINTER Coordinating Center. The structure and organization of the POINTER-NV ancillary study is well integrated with the parent trial, as shown in Figure 1, with the POINTER-NV leadership working closely with the coordinating center to provide ancillary study oversight. To align with outcome assessments in the main trial, POINTER-NV assessments are completed at baseline, Month 12, and Month 24 in a subset of parent trial participants who agree to enroll in POINTER-NV. This also aligns with the visit structure for the other three ancillary studies in U.S. POINTER that are focused on neuroimaging, sleep, and the gut microbiome, which will facilitate data coordination across the parent and ancillary studies and ultimately maximize the breadth, depth, and impact of U.S. POINTER.[10]

2.4 | Study population

The baseline characteristics of the U.S. POINTER participants have been previously reported.[23] Consistent with recruitment goals for the parent trial, which reflect the demographics of the US population as reported by the Census Bureau in 2016, POINTER-NV has a target enrollment of 50% women and at least 23% from racial and ethnic minority groups. Enrollment in the POINTER-NV ancillary study is open to all eligible U.S. POINTER participants at the four participating sites (North Carolina, California, Illinois, and Rhode Island), with plans to enroll ≈ 500 participants (250 per intervention group). Participants must be willing to come to the clinic for a separate POINTER-NV study visit to complete a neurovascular assessment. Participants with a pacemaker or a history of atrial fibrillation, as assessed by self-report at screening for the parent trial, are excluded. Given our interest in investigating associations between neurovascular outcomes and brain structure and function, we aim to enroll participants who also agree to undergo brain magnetic resonance imaging (MRI) and positron emission tomography (PET) scans as part of the POINTER Imaging ancillary study, with a co-enrollment goal of at least 50%.

2.5 | Recruitment and screening

Every effort is made to enroll U.S. POINTER participants during the parent trial's first of two baseline study visits. Interested participants receive an informational brochure, and those with continued interest are consented at the second parent trial baseline visit and scheduled for the baseline POINTER-NV study visit. The flow of participants through the parent trial and the POINTER-NV ancillary study is shown in Figure 2. To maximize enrollment, participants who have already completed baseline testing for the parent trial (e.g., before POINTER-NV is initiated at the site) may also be approached to assess their eligibility and interest in POINTER-NV, provided they have not completed their Month 12 clinic visit. In this case, interested participants are consented post-randomization and scheduled for their first POINTER-NV visit after the parent trial Month 12 clinic visit.

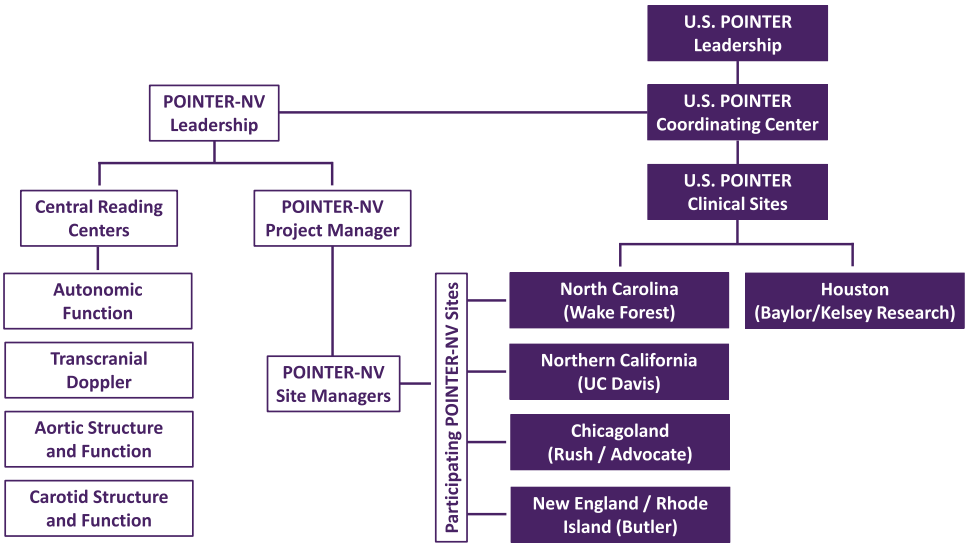

FIGURE 1 Organization and integration of the POINTER-NV ancillary study. POINTER Neurovascular, Protect Brain Health through Lifestyle Intervention to Reduce Risk–Neurovascular; UC, University of California; U.S. POINTER, U.S. Study to PrOtect Brain Health through Lifestyle INTErvention to Reduce Risk.

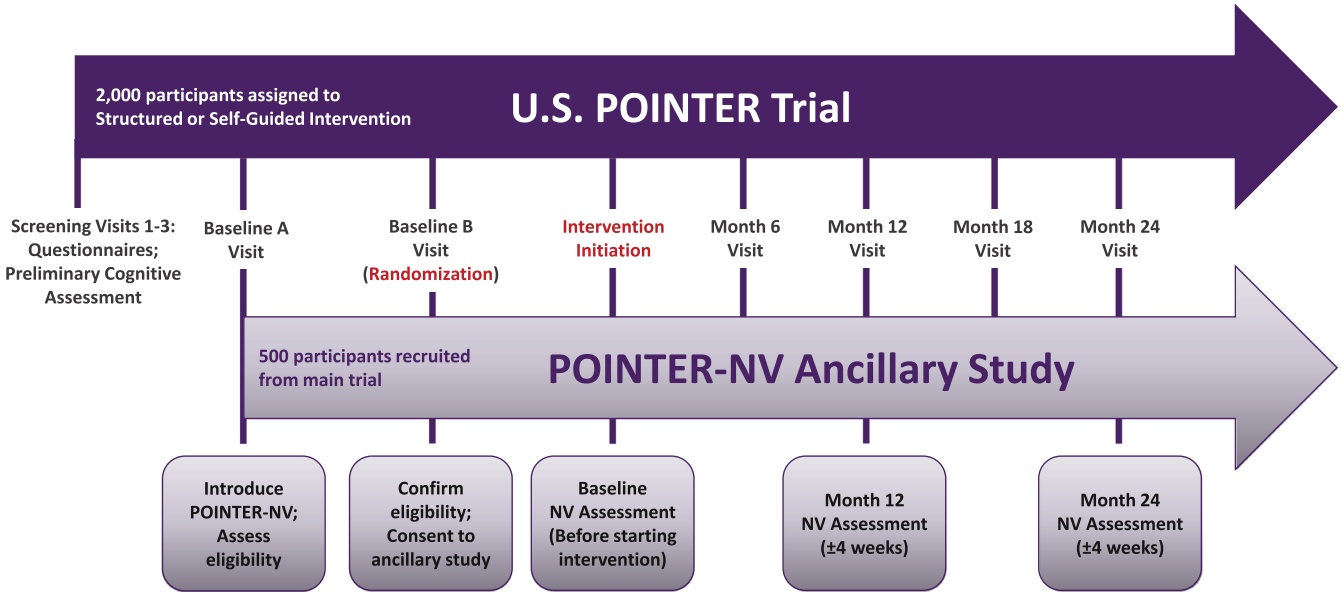

FIGURE 2 POINTER-NV participant flow. POINTER-NV, Protect Brain Health through Lifestyle Intervention to Reduce Risk–Neurovascular

2.6 | Study visits

U.S. POINTER participants who enroll in POINTER-NV are asked to complete a separate POINTER-NV study visit after the baseline, Month 12, and Month 24 parent trial clinic visits. Participants are instructed to fast for at least 4 hours and take all medications as usual prior to the POINTER-NV visit. Each visit takes ≈ 2 to 2.5 hours to complete and begins with the assessment of vascular structure and function, followed by assessment of autonomic function and cerebral hemodynamics. Prior to finalizing the step-by-step procedures for the POINTER-NV study visit, multiple practice sessions were conducted to optimize the order and timing of assessments while minimizing participant and staff burden. These assessments are described below and in the protocol (see Table S1 in supporting information). All staff conducting the assessments are blinded to intervention assignment.

2.7 | Study procedures

Vascular structure and function are assessed in the supine position using standard procedures. Supine auscultatory blood pressure measurements are obtained using a semi-automated computer-controlled device (NIHem USB Workstation, Cardiovascular Engineering).[24] Next, a custom transducer and simultaneous electrocardiography (ECG) are

used to perform applanation tonometry to obtain arterial waveforms from the carotid, femoral, and radial arteries. Transthoracic echocardiography is used to obtain parasternal long-axis views of the aorta and left ventricular outflow tract, and an apical five-chamber view is used to obtain pulsed Doppler flow waveforms from the left ventricular outflow tract. A high-frequency linear ultrasound probe is used to obtain standardized B-mode images and Doppler flow waveforms from the left and right common carotid arteries ≈ 10 to 20 mm proximal to the tip of the flow divider.[25] Hemodynamic data and ultrasound images are uploaded for offline analysis by the Aortic Structure and Function Reading Center at Cardiovascular Engineering Inc. (Norwood, MA) and the Ward A. Riley Ultrasound Center at Wake Forest.

To assess autonomic function beat-to-beat blood pressure and heart rate are recorded continuously using a continuous non-invasive arterial pressure (CNAP) system consisting of an arm cuff, a double finger cuff, and three-lead ECG (BIOPAC Systems Inc.). Measurements are made at rest in the supine, seated, and standing positions and in response to postural changes (e.g., supine to standing; seated to standing).[26] An arm sling is used to keep the hand at heart level and stabilize blood pressure recordings during movement. Bilateral transcranial Doppler (TCD; DWL) is used to assess cerebral blood velocity in the middle cerebral arteries at rest in the seated position, during a single sit-to-stand challenge, and in response to a CO_2 challenge.[27] Under most conditions the middle cerebral artery diameter is stable, and therefore changes in cerebral blood velocity are proportional to changes in cerebral blood flow.[28] To assess the cerebral blood velocity response to changes in arterial CO_2, participants are asked to breathe rapidly (i.e., hyperventilate at a rate of ≈ 1 breath per second) for up to 30 seconds, followed by 3 minutes of spontaneous breathing and then inhalation of a gas mixture containing 5% CO_2 for ≈ 3 minutes. Changes in CO_2 are monitored using a nasal cannula and capnography. All signals are simultaneously recorded using a data acquisition system (BIOPAC Systems and AcqKnowledge 5.2 software) and then uploaded for offline analysis by the Autonomic Function and TCD Reading Centers at Wake Forest.

2.8 | Standardization across sites

All clinical sites undergo rigorous training and certification procedures before enrolling participants in POINTER-NV. The ultrasound examinations are performed according to a detailed standardized protocol by trained, certified sonographers, subject to semi-annual evaluation. Each site appoints a site manager who is responsible for ensuring that the neurovascular data are collected per protocol and that all standard operating procedures are followed. As noted above, all imaging and hemodynamic data are analyzed centrally in a blinded fashion by the appropriate central reading centers. In addition, sites are provided with the specific BIOPAC, TCD, and NIHem equipment needed to conduct the neurovascular assessments and are responsible for identifying ultrasound machines and cardiac and vascular probes to use with the NIHem equipment. This further ensures robust data collection in the POINTER-NV study and allows for better data harmonization and analysis across study sites. After study launch, monthly phone calls are held to ensure consistency across sites and troubleshoot any recruitment, protocol, and equipment issues that may come up.

3 | RESULTS

3.1 | Primary outcomes

The two primary outcomes in POINTER-NV are cerebral autoregulation and baroreflex sensitivity, which reflect local and systemic mechanisms, respectively, that regulate global cerebral blood flow. Continuous blood pressure, heart rate, and cerebral blood velocity data acquired in the supine, seated, and/or standing positions are analyzed using custom MATLAB scripts for the assessment of cerebral autoregulation and Nevrokard BRS software (Nevrokard Kiauta, d.o.o.) for the assessment of autonomic function. The primary measures of cerebral autoregulation (i.e., phase shift and gain) are calculated using transfer function analysis based on changes in cerebral blood velocity in response to spontaneous fluctuations in blood pressure at seated rest in accordance with Cerebral Autoregulation Research Network (CARNet) recommendations.[29] Lower gain and higher phase are indicative of better cerebral autoregulation. Cerebral autoregulation is also assessed during a single sit-to-stand challenge (three repetitions of the following protocol: 2 minutes sitting, 1 minute standing), which invokes larger hemodynamic fluctuations and mimics a clinically relevant orthostatic challenge that is observed in normal daily activities.[27] The primary measure of baroreflex sensitivity (i.e., Sequence ALL) is calculated from the supine position using the sequence method. This method quantifies sequences of at least three beats (n) in which systolic blood pressure consecutively increases or decreases and is accompanied by changes in the same direction of the R–R interval of subsequent beats ($n + 1$).[30] The mean of all individual slopes (Sequence ALL) is then calculated, where higher values indicate greater baroreflex sensitivity. The sequence method is also applied to changes in blood pressure and heart rate in the seated and standing positions.

Additional measures of cerebral autoregulation (e.g., autoregulatory index and the rate of recovery), baroreflex sensitivity (e.g., low-frequency and high-frequency alpha indexes), and autonomic function (e.g., heart rate variability, blood pressure variability, sympathovagal balance, and orthostatic hypotension) are also derived, as previously described. In brief, the autoregulatory index is determined using hypothetical response curves with values ranging from 0 to 9,[31] while rate of recovery is defined by the speed at which cerebral blood velocity returns to baseline.[27] In both cases, higher values are indicative of better cerebral autoregulation. Secondary indices of baroreflex sensitivity, blood pressure variability, and heart rate variability are calculated both in the frequency domain using power spectral analysis and in the time domain.[30,32] Sympathovagal balance is calculated as the ratio of spectral powers for beat-to-beat R–R intervals in the low-frequency versus high-frequency ranges. Orthostatic hypotension is measured from continuous blood pressure monitoring during the transition from supine to standing and is defined as a significant drop in

blood pressure (≥20 mmHg for systolic, ≥10 mmHg for diastolic) within 3 minutes of standing in accordance with the Consensus Committee of the American Autonomic Society and the American Academy of Neurology.[33]

3.2 | Secondary outcomes

Secondary outcomes include measures of vascular structure and function assessed at multiple levels: the aorta, carotid arteries, and middle cerebral arteries. Blood pressure, ECG, tonometry, and ultrasound data are digitized during the primary acquisition and analyzed using customized software to obtain measures of aortic and carotid diameter, pressure, mean/peak flow, and impedance.[24] Additionally, the pressure and flow waveforms are used to assess impedance matching and wave reflection at the aorta–carotid interface. Outcomes of interest include carotid–femoral pulse wave velocity (PWV), the gold-standard measure of aortic stiffness,[34] as well as measures of carotid pulsatility, aorta–carotid reflection coefficient, and carotid transmission coefficient, which reflect transmission of pulsatile flow into the cerebral vasculature.[24]

Carotid IMT is measured in the common carotid artery using standardized procedures. Dedicated imaging analysis software (Image-Pro, Media Cybernetics) is used to measure the maximum IMT of the near and far walls of the left and right common carotid arteries at defined interrogation angles in accordance with recommendations from the American Society of Echocardiography CIMT Task Force.[35] Carotid stiffness is measured using cardiac cycle-dependent changes in common carotid artery diameter (via ultrasound) and corresponding changes in carotid blood pressure (via tonometry).[25] Standard formulas are used to calculate a variety of indices (e.g., distensibility, compliance, Young elastic modulus, and β-stiffness index) using Carotid Studio software (Cardiovascular Suite, Quipu).[36,37]

Cerebral blood velocity in the middle cerebral arteries is analyzed using DWL's automated waveform tracking software (QL software). Changes in cerebral blood velocity in response to hypocapnia and hypercapnia, along with corresponding changes in end-tidal CO_2, are assessed to calculate cerebral vasomotor range (i.e., the absolute change in cerebral blood velocity from hypocapnia to hypercapnia) and cerebral vasomotor reactivity (i.e., the percent change in cerebral blood velocity relative to the baseline value).[38] Other relevant measures of cerebral hemodynamics including cerebrovascular resistance index, pulsatility index, critical closing pressure, and resistance-area product are also calculated.[38–40] The latter two metrics are derived from the instantaneous pressure–velocity relationship for each cardiac cycle and are thought to reflect the myogenic and flow-mediated pathways underlying dynamic cerebral autoregulation responses.[40]

3.3 | Power and sample size determination

Our primary objective is to test whether lifestyle modification improves neurovascular outcomes. The targeted sample size ($N = 500$) was chosen to provide adequate power to detect intervention group differences in the two primary outcomes: baroreflex sensitivity and cerebral autoregulation. Power estimates were calculated based on 5-month differences in baseline standard deviation (SD) units for resting measures of baroreflex sensitivity and cerebral autoregulation using unpublished data and a variety of reports from case–control and intervention studies.[17,26,41] Simulated power estimates (from 250 simulated data sets) were based on various assumptions of detectable effect size, within-subject correlation for repeated measures of $r = 0.70$ for baroreflex sensitivity and $r = 0.81$ for cerebral autoregulation (with an autoregressive 1 structure), a loss to follow-up rate of 20% over 2 years, and an overall type 1 error rate of 0.05 (Bonferroni-adjusted for two primary outcomes). Additionally, we assumed that at least 300 participants would be enrolled at baseline to provide data at three time points (baseline, Month 12, and Month 24), that ≈ 200 participants would be enrolled at Month 12 to provide data at two time points (Month 12 and Month 24), and that an intervention effect would be observed at Month 12 and maintained through Month 24. Simulations indicated that the targeted sample of $N = 500$ will provide at least 90% power to detect an effect size as small as 0.285 SD for baroreflex sensitivity and 82% power to detect an effect size as small as 0.3 SD for cerebral autoregulation. These estimates also apply to analysis of the intervention effect on secondary outcomes, including additional measures of autonomic function and measures of vascular structure and function. The power calculations to address these secondary outcomes do not adjust for multiple comparisons because they were chosen to better understand the implications of the findings from the primary analysis. Power calculations to assess the degree to which longitudinal and intervention effects on neurovascular outcomes predict changes in cognitive function (i.e., global and domain-specific composite scores) and brain structure and function (e.g., cerebral blood flow and white matter hyperintensity volume on MRI; amyloid and tau pathology on PET) use the same assumptions (e.g., loss to follow-up rate) and analytic model as described above and indicate a power of 85% to detect a correlation as low as 0.15 for a total sample size of 500.

3.4 | Statistical analysis

The primary analysis will be based on the intention-to-treat approach in which data from all participants are analyzed according to their original intervention assignment. Mixed effects models for repeated measures will be used with Bonferroni adjustment to examine differences in baroreflex sensitivity and cerebral autoregulation between intervention groups based on a two-sided test at an overall significance level of 0.05. Covariates will include age, sex, race, ethnicity, site (stratification factor), and visit (Baseline, Month 12, Month 24) to control for potentially non-linear effects of the interventions. Within-subject correlation will be parameterized using a compound symmetry structure. We will use linear contrasts to examine differences in mean follow-up values versus baseline values between intervention groups. These models will allow for baseline data to be missing for some participants, which will be assumed to be missing at random as would be expected by the enrollment plan and randomization process.[42]

Inverse probability weighting will be used to gauge the influence of missing data on our results and, if warranted, multiple imputation will be used in sensitivity analyses to generate adjusted estimates.

A similar approach will be used to analyze secondary outcomes, including aortic stiffness, carotid stiffness, carotid IMT, and cerebral vasomotor reactivity. No adjustments for multiple comparisons will be made in these analyses; however, all results will be reported with unadjusted *P* values, point estimates, and 95% confidence intervals. We will also examine the degree to which longitudinal changes in neurovascular outcomes are associated with changes in cognitive and neuroimaging outcomes using mixed effects models. Changes in baroreflex sensitivity, cerebral autoregulation, aortic stiffness, carotid stiffness, carotid IMT, cerebral vasomotor reactivity, and other hemodynamic measures over time will be regressed on the change in key brain outcomes (i.e., cognitive function, brain structure and function). Covariates are prespecified to include intervention assignment, age, sex, race, ethnicity, and site. Other factors (e.g., hypertension, diabetes status, and baseline blood pressure) may influence outcomes, and while these are expected to be balanced between intervention groups due to the randomized design, it will be important to assess their impact on the results. To do so, we will conduct sensitivity analyses fitting models with additional covariate adjustments.

3.5 | Safety monitoring and reporting

Adverse events (AEs) that may occur as a result of participation in the POINTER-NV study are explained during the consenting process, and participants are instructed on how to alert study personnel if and when these occur. In collaboration with the parent trial, the U.S. POINTER study clinician reviews, evaluates, and reports all POINTER-NV AEs and serious adverse events (SAEs) to a safety committee. An external data and safety monitoring board also monitors participant safety and reviews information on AEs, SAEs, and incidental findings on a regular basis.

3.6 | Data monitoring and management

The Data Coordinating Center for U.S. POINTER oversees data collection and management for the main trial and all the ancillary studies, as described previously.[10] In brief, mechanisms to facilitate integration of POINTER-NV into parent trial operations include expansion of the U.S. POINTER database to accommodate tracking and data collection for POINTER-NV, development of site-specific tools for recruitment into POINTER-NV, and support for the implementation of POINTER-NV protocols across participating sites.

4 | DISCUSSION

Through its comprehensive assessment of baroreflex sensitivity and cerebral autoregulation, POINTER-NV will be the first study to examine the effects of a multidomain lifestyle intervention on these key neurovascular mechanisms and their longitudinal associations with cognitive and brain health. POINTER-NV offers several unique aspects, as there are currently no studies that focus on the two major pathways that regulate cerebral blood flow, along with a variety of measures reflecting autonomic function and vascular structure and function, at multiple levels of the vasculature. Notably, POINTER-NV is examining commonly studied vascular health measures (e.g., arterial stiffness, carotid IMT), measures that are generally understudied in the context of ADRD (e.g., baroreflex sensitivity and cerebral autoregulation), as well as more innovative measures of pulsatile flow (e.g., aorta–carotid wave reflection, carotid transmission coefficient) to identify the most relevant biomarkers for ADRD in a racially and geographically diverse population of at-risk older adults.

Despite growing evidence that the arterial baroreflex and cerebral autoregulatory responses can impact brain health, few ADRD studies have assessed the role of these upstream regulators of cerebral blood flow.[13] It has recently been shown that baroreflex sensitivity and other measures of autonomic function such as heart rate variability and sympathovagal balance are independent risk factors for dementia.[43,44] Measures of vascular structure and function, including carotid–femoral PWV, carotid distensibility, and carotid IMT have also been shown to predict incident dementia.[45,46] However, to our knowledge, there are few prospective studies linking cerebral autoregulation or cerebral vasomotor reactivity to dementia outcomes, especially in the context of a lifestyle intervention. There are also limited data on the association between neurovascular measures and dementia subtypes, including AD and vascular dementia. Although incidence of ADRD is not a prespecified outcome in the parent trial, the neurovascular assessments will help to elucidate underlying mechanisms that can influence cognitive trajectory and risk for ADRD. For example, the use of TCD to assess cerebral blood velocity provides a clinically relevant technique with high temporal resolution,[47,48] which will complement the high spatial resolution of MRI-based measures of cerebral blood flow obtained as part of the POINTER Imaging ancillary study.[49] In addition, the non-invasive measures of vascular hemodynamics can be used in conjunction with the MRI-based measures of white matter hyperintensity volume and the PET-based measures of amyloid and tau pathology to clarify associations with dementia subtypes.

Impaired autonomic function, as evidenced by low baroreflex sensitivity and/or low heart rate variability, is common in older adults and dementia patients[50,51] and is associated with impaired or reduced cognitive function,[52,53] hippocampal perfusion,[54] cortical thickness,[55] and white matter integrity.[56] Several lines of evidence also suggest that brain areas involved in autonomic control are among the first to be affected by neurodegenerative changes.[57,58] As such, autonomic dysfunction may be present at a "preclinical stage," that is, prior to the onset of clinical symptoms, and thereby offer an early and relatively easy to assess biomarker of neurodegeneration. On the other hand, data on cerebral autoregulation in AD are less clear. Lower cerebral autoregulation has been associated with greater amyloid uptake on PET and greater white matter hyperintensity volume on MRI in older adults without dementia;[59] however, data from case–control

studies are mixed, suggesting that cerebral autoregulation may or may not be impaired in patients with mild cognitive impairment (MCI) and AD.[26,38,60,61] It should be noted that prior studies are limited by small sample sizes, cross-sectional designs, incomplete assessment of relevant hemodynamic changes, and simplistic analysis of cerebral autoregulation. POINTER-NV will overcome limitations of prior studies to address key gaps in the field.

Cerebrovascular dysfunction may contribute to impaired augmentation of cerebral blood flow in response to a physiological stimulus. Altered cerebral vasomotor reactivity has been largely attributed to the harmful effects of increased pulse pressure (caused by aortic and carotid artery stiffness), increased cerebral microvascular resistance (caused by cerebrovascular remodeling or damage, impaired vasodilatory responses, or sustained vasoconstriction), and reduced wave reflection at the aorta–carotid interface (caused by impedance matching) leading to enhanced transmission of harmful pulsatile power into the microcirculation.[62–64] Cerebrovascular dysfunction occurs with advancing age, even before the development of brain atrophy, amyloid accumulation, and cognitive decline. Notably, lower resting cerebral blood flow, impaired cerebral vasomotor reactivity, and increased cerebrovascular resistance have been observed in patients with ADRD compared to controls and may predict future cognitive decline and progression of MCI to dementia.[39,60,61,65] POINTER-NV will be the first trial to investigate the complex interactions between the central nervous system and the systemic vasculature in older adults who are cognitively normal at baseline, but at increased risk for ADRD.

Maintaining blood pressure during postural changes is important for cerebral perfusion and becomes increasingly difficult with advancing age. Indeed, orthostatic hypotension is prevalent in older adults and is associated with cognitive impairment and dementia.[66,67] A large body of evidence suggests that if excessive decreases in blood pressure upon standing, coupled with increased short-term blood pressure variability and an attenuated heart rate response, occur in the presence of blunted cerebral autoregulation and increased arterial stiffness, this combination may render the brain more susceptible to intermittent hypoperfusion.[68–70] These findings highlight the importance of using orthostatic challenges and conducting comprehensive hemodynamic assessments to identify key deficits that promote cerebral hypoperfusion and subsequent cognitive decline. By measuring heart rate, blood pressure, and cerebral blood velocity continuously throughout a variety of postural changes, POINTER-NV will advance our understanding of how autonomic and autoregulatory mechanisms modulate cardiovascular hemodynamics in response to normal daily activities and how these responses correlate with biomarkers of brain health. Moreover, knowing the status of cerebral autoregulation, baroreflex sensitivity, and orthostatic hypertension in a population like U.S. POINTER may potentially allow for better risk stratification and more personalized treatment approaches.

Lifestyle interventions may have profound effects on autonomic and vascular function. For example, regular exercise has well-known benefits on autonomic and vascular function and has been associated with lower arterial stiffness and higher baroreflex sensitivity, heart rate variability, and cerebral vasomotor reactivity.[13–15,20,71] Diet also plays a critical role in brain health,[72] and both the DASH and Mediterranean diets have been shown to improve or attenuate age-related changes in several of the neurovascular outcomes studied in POINTER-NV.[16,21,22] As important contributors to cerebral blood flow, neurovascular mechanisms may be useful intervention targets to reduce the risk of cognitive decline and dementia. With longitudinal assessments captured before and up to 2 years after one of two different lifestyle interventions, the design of the U.S. POINTER trial provides an unprecedented opportunity to determine whether neurovascular mechanisms are modifiable and correlate with changes in cognitive and neuroimaging outcomes in an at-risk population of older adults.

In sum, successful completion of the POINTER-NV study will yield important information about local and systemic mechanisms that regulate cerebral blood flow in older adults at risk for ADRD. The investigation of these key neurovascular outcomes in the context of the U.S. POINTER trial is particularly exciting. POINTER-NV will be the first study of its kind, providing an integrated, multi-level view of brain–body connections linking neural and vascular pathways that impact ADRD-related outcomes. In collaboration with the main trial and the POINTER Imaging ancillary study, POINTER-NV will be the largest trial to date to assess the effects of a multimodal lifestyle intervention on both central and peripheral vascular contributions to ADRD. Ultimately, the findings of this study may shed light on the potential impact of intensive prevention strategies for dementia, even beyond lifestyle changes, which can be used to inform the development of targeted therapeutic approaches to treat traditional and non-traditional vascular risk factors.

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CONFLICT OF INTEREST STATEMENT

Heather Snyder is a full-time employee of the Alzheimer's Association. Gary Mitchell is the owner of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. Dr. Mitchell also serves as a consultant to and receives grants and honoraria from Novartis, Merck, Bayer, Servier, Philips, and deCODE genetics, and he is an inventor on pending patent applications that disclose methods for predicting various measures of biologic age using pressure waveforms and a convolutional neural network. All other authors have no conflicts to report. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provide written informed consent to participate in this study.

ORCID

Tina E. Brinkley https://orcid.org/0000-0002-1905-758X

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SUPPORTING INFORMATION

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

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