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RESEARCH ARTICLE

Baseline characterization of the ARMADA (Assessing Reliable Measurement in Alzheimer's Disease) study cohorts

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Abstract

Introduction: The National Institutes of Health (NIH) Toolbox (NIHTB) provides computerized measures of cognition, emotion, sensation, and motor abilities across the lifespan. The ARMADA (Assessing Reliable Measurement in Alzheimer's Disease and Cognitive Aging) study validated the NIHTB in individuals across the cognitive aging spectrum. This article reports the characteristics of our sample of participants.

Methods: Participants were recruited across nine sites and classified clinically as cognitively normal (NC), with mild cognitive impairment (MCI), or with dementia of the Alzheimer's type (DAT.) They completed the NIHTB at multiple time points and many had at least one Alzheimer's biomarker previously obtained.

Results: Groups differed with respect to dementia severity levels, as anticipated, but were well-matched across many demographic characteristics.

Discussion: The ARMADA study demographics and baseline characteristics provide a suitable sample for validating the NIHTB across the cognitive aging spectrum. Other enriched samples (African American participants, Spanish NIHTB, 85+ years of age) will be reported elsewhere.

KEYWORDS
aging, Alzheimer's disease, cognition, dementia, mild cognitive impairment, NIH Toolbox

Highlights

- There is a need for assessments that can detect the early stages of cognitive decline in older adults.
- The ARMADA (Assessing Reliable Measurement in Alzheimer's Disease and Cognitive Aging) study will validate the National Institutes of Health (NIH) Toolbox across the aging spectrum, including mild cognitive impairment (MCI) and dementia of the Alzheimer's type (DAT).
- Here we report the characteristics of participants.

- Groups were well-matched across most demographic characteristics, and clinical characteristics differed as expected.
- ARMADA study cohorts reflect their respective clinical syndromes for validating the NIH Toolbox.

1 | INTRODUCTION

The prevalence of cognitive decline in older adults is rising at a never-before seen rate, due to both the growing population of aging adults and to new medical advances that are leading to longer average life expectancies. It is currently projected that by 2030, individuals over the age of 65 will comprise more than 20% of the total population in the United States, a 4% increase compared to 2020.[1] In addition, the number of individuals with dementia worldwide is expected to increase substantially (up to 3-fold) by 2050.[2] The leading cause of progressive cognitive decline in individuals over the age of 65, alone or in combination with other diseases[3] is Alzheimer's disease (AD). AD is a neurodegenerative brain disease that typically presents clinically as an amnestic cognitive syndrome progressing over years to final stages referred to as dementia of the Alzheimer's type (DAT).[4] The term "dementia" (currently referred to as a major neurocognitive disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5][5]) connotes cognitive change that exceeds what is expected in the course of "normal aging" to the point of interfering with independent activities of daily living such as driving, managing finances, meal preparation, or grooming. Mild cognitive impairment (MCI) is a term that refers to the prodromal state of DAT, at a time when biomarkers for AD are present and cognitive impairments exceed "normal" age-related decline, but are not yet significantly interfering with most activities of daily living. [6,7]

Given the increasing rates of clinical MCI and dementia, there is a great need for early detection of prognostic cognitive decline in older adults. Although there is currently no "cure" for neurodegenerative conditions, early detection allows for earlier treatment, which can slow symptom progression[8] and may help affected individuals and caregivers with future care planning. Unfortunately, at present, identifying or diagnosing a clinical dementia, especially in very early stages, can only be accomplished through lengthy neuropsychological evaluations that may not be available to all individuals and are not always suitable for widescale use. Although brief cognitive screening tests exist, they tend not to be sufficiently sensitive to detect mild deficits.[9] Most critically, the field lacks appropriate assessments and normative data for individuals in racially, ethnically, and linguistically diverse groups.[10,11]

To address these challenges, the National Institutes of Health (NIH) Toolbox for Assessment of Neurological and Behavioral Function (NIHTB)[12,13] could serve as an effective intermediate method for detecting cognitive decline in older adults, and assessing domains beyond cognition that may mark other factors associated with dementia (e.g., aspects of emotion, sensation, and motor abilities).[14] The goal of the present study, ARMADA (Assessing Reliable Measurement in Alzheimer's Disease and Cognitive Aging), was to validate the four modules of the NIHTB among adults age 65 and older across groups with normal cognition (NC), amnestic MCI, or early (mild) DAT. The methods for this study are described in detail in a prior publication[15] and the present report provides detailed characteristics of the study populations. Participants were drawn from established research cohorts across nine sites with existing cohorts of older adults along the cognitive aging spectrum. Research group diagnosis had been characterized prior to study enrollment by the sites (maximum of a 3-month window between ARMADA study visit and corresponding diagnosis visit), and AD biomarkers were available for a portion of participants. Three additional samples were also recruited: one consisted of cognitively normal individuals age 85 and older; the second was an enriched sample of African Americans; and the third consisted of Spanish-speaking individuals who were administered the Spanish version of the NIHTB. These additional samples were enrolled in order to expand normative data for these populations and to help address existing disparities in assessment research. This article describes the demographic and clinical characteristics of participants ages 65 to 84 from our research volunteer sample. The description of special emphasis groups, including participants 85 and older, African American individuals, and Spanish-Speaking individuals, will be presented elsewhere.

2 | METHODS

2.1 | Recruitment sites

For detailed information regarding study methods, refer to Weintraub et al.[15] Participants in the cognitively normal control (NC), MCI, and DAT groups were recruited from existing cohorts across sites that are Alzheimer's Disease Research Centers (ADRCs), as well as affiliated sites with longitudinal studies of normal and cognitively impaired older adults that utilized assessment and diagnostic methods similar to those employed by the ADRCs. The sites included: Northwestern University (lead site); University of Michigan; University of Wisconsin-Madison; Mayo Clinic-Jacksonville, Florida; University of Pittsburgh; Emory University; University of California San Diego; Columbia University; and Massachusetts General Hospital. Many of the sites had imaging and cerebrospinal fluid (CSF) biomarkers of AD neuropathology available on a portion of their cohorts, as well as genotypes of AD risk. A majority of sites had utilized the Uniform Data Set (UDS),[16–18] methodology to characterize and diagnose participants prior to their recruitment for the ARMADA study. For more recruitment and enrollment details per site, refer to Table 1.

2.2 | Overview of diagnostic and inclusion/exclusion criteria

Research group diagnosis was established using UDS methodology through the National Alzheimer's Coordinating Center (NACC; https://www.alz.washington.edu/WEB/forms_uds.html), which maintains a large database of clinical and neuropathological data and implements guidelines for clinical diagnosis based on up-to-date research. Diagnosis was established using the Clinical Dementia Rating (CDR) scale,[19] Functional Activities Questionnaire (FAQ),[20] the UDS neuropsychological battery or comparable cognitive tests for each domain captured in the UDS, as well as other relevant clinical data. Participant characteristics and data were obtained from the participant, study partner, neuropsychological testing, neurological examination, and additional neuroimaging or laboratory data as available. A majority of sites carried out research consensus conferences in the diagnostic process. Diagnoses for participants recruited outside of the ADRCs, that is, in affiliated studies, used similar criteria.

Participants in the two groups with cognitive impairment included individuals age 65 and older with a research diagnosis of DAT (global CDR score of ≈1.0) or aMCI (amnestic single or multidomain; global CDR score of ≈0.5) using the 2011 National Institute on Aging–Alzheimer's Association (NIA-AA) criteria.[21,22] DAT is defined on the basis of progressive cognitive impairment, with prominent memory loss and additional cognitive deficits that represent a decline from previous functioning, and interfere with the ability to function in daily activities. We included individuals with mild DAT because, although we have not administered the NIHTB in participants at more advanced stages of dementia, it is our suspicion that these individuals would have more difficulty completing the NIHTB. MCI is defined as impairment in one or more cognitive domains with preservation of independence in functional abilities. Participants with aMCI (single or multidomain) were included, as this clinical profile is most associated with Alzheimer's neuropathology.[6] Participants with non-amnestic MCI were not included. The diagnostic procedures included prediction of primary and contributing etiologies based on currently known probabilities of association between clinical features and neuropathologic findings at postmortem brain autopsy.[23] Biomarker information was also available in some instances to further strengthen the suspected etiology. Exclusion criteria included: (1) medical conditions that may negatively affect cognitive functioning, including history of central nervous system (CNS) disease (e.g., toxic/metabolic encephalopathy, normal pressure hydrocephalus, stroke, brain tumor), (2) history of a chronic major psychiatric disorder, or (3) alcohol or other substance abuse.

Cognitively normal individuals were recruited and enrolled using similar methods. This group included individuals ages 65 to 84, without significant complaints of cognitive decline, including memory loss, and with NC as assessed by standard cognitive testing, study partner report, and other clinical data obtained with the UDS or similar research procedures. Cognitively normal participants were required to live independently, without difficulties carrying out activities of daily living. Exclusion criteria, in addition to those for the MCI and DAT groups, included serious medical conditions that may affect cognitive functioning (e.g., thyroid disorder, renal, hepatic, cardiac or pulmonary insufficiency, unstable diabetes, uncontrolled hypertension, cancer, or chronic use of neuroleptic or hypnotic medications) at the site investigator's discretion. Participants were not excluded if they had conditions such as hypertension or diabetes that were well controlled or they were taking antidepressants or anxiolytics for situational symptoms and symptoms were well controlled.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources, such as PubMed. The literature review included background on the cognitive aging spectrum, including mild cognitive impairment (MCI) and dementia of the Alzheimer's type (DAT), as well as the methods used to quantify cognitive impairment in these populations. Relevant citations are cited appropriately.
2. **Interpretation**: This article describes the demographic and clinical characteristics of the ARMADA (Assessing Reliable Measurement in Alzheimer's Disease and Cognitive Aging) study, which aims to validate the (National Institutes of Health (NIH) Toolbox across the cognitive aging spectrum, including normal aging, MCI, and DAT.
3. **Future directions**: Future studies will evaluate differences across all four modules of the NIH Toolbox across groups, examine the relationship between performance and biomarkers, and assess performance longitudinally. In addition, there are special emphasis cohorts, which include individuals age 85 and older, African American participants, and Spanish-speaking participants.

2.3 | Brief overview of NIH Toolbox, UDS neuropsychological battery, clinical data, and biomarker data collection

Participants completed NIHTB assessments at baseline, and were subsequently followed at 12 and 24 months. The study was significantly disrupted by the coronavirus disease 2019 (COVID-19) pandemic, which emerged just as the baseline recruitment was drawing to a close. As a result, we were not able to establish sufficient power for analysis of the 24-month data but will be able to analyze 12-month data in some of the groups. With few exceptions, participants received all four modules of the NIHTB. The cognition battery consists of tests assessing executive function and attention, episodic memory, language, processing speed, and working memory. The emotion battery consists of self-report surveys of multiple areas of emotional functioning. The motor battery assesses dexterity, grip strength, standing balance, locomotion, and endurance. The sensation battery assesses audition, vision, olfaction, and pain. For more details on each module, refer to the original publications[13,24–33] and the NIHTB website (nihtoolbox.org).

TABLE 1 Summary of recruitment and enrollment methods across sites

ARMADA SITE	Recruitment methods	Diagnostic methods
Columbia University	Recruited through WHICAP study, a multi-ethnic cohort of community-living participants followed longitudinally.	Core assessment includes standardized interviews, neurologic and neuropsychological exams, and biomarker studies. Diagnosis is confirmed by consensus conference with multiple research clinicians, who are blind to biomarker status and blind to prior diagnosis.
Emory University	ADRC Clinical Core, often identified during consensus conference, and Biomarker Initiative consisting of patients seen in the Cognitive Neurology Clinic.	UDS procedures and NACC guidelines; UDS demographic and diagnosis forms, notes for annual visits, and biomarkers if available. Diagnosis was reached by Consensus Conference for ADRC participants, and by cognitive neurologist diagnosis for those in the Biomarker Initiative.
Massachusetts General Hospital	ADRC Clinical Core, Harvard Aging Brain Study, EARLY and LEARN studies; prioritized participants with amyloid PET imaging.	UDS procedures and NACC guidelines; standardized clinical ratings, cognitive testing, and neurologic exam. Initial diagnosis determined by clinician-related CDR, and consensus conference was consulted is discrepancy from previous year.
Mayo Clinic Jacksonville	Community events, concurrent studies within NIA-funded ADRC, referrals from behavioral neurology department, Mayo Older African Americans Normative Studies	UDS procedures and NACC guidelines; standardized interviews, neurologic and neuropsychological exams, and biomarker studies. Initial diagnosis rendered by neurologist and confirmed with diagnostic case consensus conference.
Northwestern University	ADRC Clinical Core, Neurobehavior and Memory Clinic, and center's recruitment registry.	UDS procedures and NACC guidelines; standardized interviews, neurologic and neuropsychological exams, and biomarker studies. For patients referred through the Neurobehavior and Memory Clinic, referral information and cognitive testing from clinician was provided. Diagnosis confirmed either by clinician or consensus conference with multiple research clinicians.
University of California, San Diego	ADRC longitudinal study cohort and recruitment sessions during memory screening events in the community	UDS procedures and NACC guidelines; self-report questionnaires, interviews, cognitive exam, and neuroimaging when available. Diagnosis reached by research diagnostic consensus via neurologists in Clinical Core.
University of Michigan	ADRC longitudinal cohort (UM Memory and Aging Project, UM-MAP), Michigan ADRC Registry, and UM clinics and local communities.	UDS procedures and NACC guidelines. Formal panel determined research consensus diagnosis.
University of Pittsburgh	Parent study staff informed participants at parent study visits on-site or via phone.	CDR & GDS, neurological exam, neuropsychological testing, and neuroimaging by the parent studies; NPI-Q, FAQ, Hachinski, UPDRS in some studies. Diagnosis confirmed via diagnostic consensus conference.
University of Wisconsin-Madison	ADRC Clinical Core study (prioritizing participants with biomarkers), ADRC recruitment and educational events, local senior centers, retirement homes, local memory clinics, and recruitment registry.	UDS procedures and NACC guidelines; cognitive testing, CDR, and clinician reports. For participants in the Clinical Core, consensus conferences with multiple clinicians confirmed diagnosis. For other participants, single clinician consensus determined diagnosis.

The participants recruited from each site had been studied systematically to assign research diagnoses. Those recruited from the clinical cores of ADRCs had completed the UDS.[16–18] The UDS includes a neuropsychological battery, which measures attention span, processing speed, executive attention, category and letter fluency, object naming, visual constructions, and immediate and delayed memory. Those recruited from non-UDS sites contributed data that was comparable to that collected in the UDS including participant demographics, medical history and medications, family history, research neurological examination, dementia severity level, functional ability assessment, and behavioral and psychiatric symptoms. Non-UDS sites administered a comparable battery of neuropsychological tests

covering similar cognitive domains. All sites implemented UDS guidelines for clinical diagnosis. https://files.alz.washington.edu/documentation/uds3-ivp-guidebook.pdf

Although biomarkers were not collected prospectively as part of the ARMADA procedures, study sites contributed data on available biomarkers, including amyloid positron emission tomography (PET) and/or CSF tau/amyloid levels. Information about the apolipoprotein E (*APOE*) genotype, a major genetic risk factor for AD, was also collected where available. We recorded the availability of structural neuroimaging on each participant at each site for future identification of these resources by investigators interested in accessing these data site by site (see Table 5 for biomarker availability by study group).

2.4 | Statistical analysis

Differences in demographic variables and clinical characteristics were evaluated using chi-square tests for categorical variables, and univariate one-way analyses of variance (ANOVAs) for continuous variables. In many cases the distributions were parametric. In the cases where they were not, robust tests were conducted (e.g., Welch's *t*-test rather than the conventional Student's *t*-test). To preserve the maximum number of data points, we used pairwise deletion across the variables in question. Where there were statistically significant differences (p-values < 0.05), post hoc tests were conducted using Bonferroni corrections for categorical variables and Tukey's Honestly Significant Differences for continuous variables. Differences in performance on the NIHTB will be presented separately.

3 | RESULTS

3.1 | Demographic characteristics

The final sample included 326 participants, age 65 and older collected across nine sites. As noted in preceding text, this sample does not include individuals from the three special emphasis cohorts (Spanish-speaking, African American, 85+ years of age), which will be described in separate publications. There were three groups, ranging from NC to amnestic MCI to mild dementia presumed to be of the Alzheimer's type (DAT). Groups within this sample were well matched on the majority of demographic characteristics (Table 2) including race, ethnicity, English as primary language status, handedness, and education. Of note, the sample was highly educated overall. Post hoc comparisons revealed slight differences between the groups with respect to age (NC group was younger than MCI and DAT) and sex (NC had fewer male participants than did MCI and DAT). Nevertheless, the demographics of our sample were well matched across groups, and roughly matched to the US census.[34]

3.2 | Clinical characteristics

Dementia severity across the three groups was characterized from a combination of CDR scores and Functional Assessment Questionnaire ratings (Table 3). The CDR is a widely used 5-point scale that characterizes multiple domains of cognitive and functional abilities, with zero being normal and three indicating severe dementia, as rated based on clinical judgment. The CDR was designed specifically with DAT in mind and so the global CDR rating is heavily weighted for memory loss. The FAQ is a survey completed by the informant that classifies functional abilities into four levels: (1) normal, (2) independent but has difficulty, (3) requires assistance, and (4) fully dependent. As expected, the DAT group scored significantly higher (with higher scores indicating greater impairment) compared to the MCI and NC groups on the CDR and FAQ, and the MCI group scored significantly higher than the NC group for the CDR and FAQ. Specifically, the DAT group demonstrated greater cognitive changes (i.e., memory, problem solving, and so on) across multiple domains and poorer functional abilities compared to the other groups. Conversely, the MCI group was characterized by some degree of cognitive change (namely memory) and minimal changes in functional abilities. Cognitively normal controls demonstrated minimal cognitive or functional deficits. Performance on a measure of general cognitive ability, the Montreal Cognitive Assessment (MoCA) differed across groups, with the highest score in the NC group, followed by the MCI and DAT groups. Reported medication use, including treatments for cardiovascular and psychological conditions and AD symptoms, was available for a subset of participants (see Supplemental Table).

According to the Neuropsychiatric Inventory Questionnaire (NPIQ),[35] an informant report of neuropsychiatric symptoms manifested in the last month prior to testing, individuals in the DAT group was more likely to experience symptoms compared to individuals in the other two clinical groups (Table 4). In addition, the total number of behaviors endorsed on the NPIQ, which ranged from 0 to 12, was significantly higher for participants in the DAT group compared to those in the NC or MCI groups. The most commonly endorsed symptoms in the DAT group included apathy, depression, and anxiety. On the Geriatric Depression Scale (GDS–Short Form),[36] which is a self-report questionnaire of symptoms of depression, there were no differences between groups and mean scores in all groups were in the nondepressed range(Table 4).

3.3 | Family history

A total of 223 participants reported on whether they had a family history of cognitive impairment. Across the entire sample, 147 participants indicated that they had a first-degree family member with cognitive impairment. Prevalence of family history of cognitive impairment did not differ by participant group: χ^2 (2, $N = 223$) = 2.78, $p = 0.25$.

3.4 | Biomarkers

Although not part of data collection for ARMADA, some sites collected biomarker data, including amyloid PET and CSF tau/amyloid levels, from participants as part of other protocols in which they had

TABLE 2 Demographic characteristics

Demographic	NC (*N* = 160)	MCI (*N* = 97)	DAT (*N* = 69)	*p*-value
Mean age, years (SD)[a]	72.72 (5.08)	77.14 (7.34)	75.7 (7.22)	$p < 0.001$
Male[a]	33.8	58.8	58	$p < 0.01$
Hispanic	1.9	3.1	4.3	$p = 0.59$
White	84.1	83.5	92.8	$p = 0.14$
African American	14.6	2.5	9.6	p = 0.28
American Indian or Alaska Native	1.3	0	0	p = 0.50
Asian	0%	1	0	$p = 0.31$
Primary English lang.	99.4	100	97.1	$p = 0.15$
Education				
High school or less	4.3	3.6	11.9	$p < 0.01$
Some college	11.7	19.3	20.9	
College	31.9	31.3	37.3	
Graduate	52.1	45.8	29.9	
Right-handed	90.6	87.6	88.4	$p = 0.73$

Note: Data are percentages unless indicated otherwise. Although a chi-square test indicated that the three clinical groups differed in education, follow-up post hoc tests correcting for multiple comparisons did not yield significant differences.
Abbreviations: DAT, dementia of the Alzheimer type; MCI, individuals with mild cognitive impairment; NC, cognitively normal older control participants; all clinical categories based on research clinical diagnostic criteria. Lang = language.
[a]Indicates differences in demographic characteristic by clinical group $p < 0.05$, and confirmed by post hoc tests using Bonferroni correction for multiple comparisons.

TABLE 3 Clinical dementia ratings by domain, MoCA scores, and FAQ scores

	NC	MCI	DAT	*p*-value
CDR Domain, mean (SD)				
Memory[a]	0.14 (0.26)	0.64 (0.28)	1.09 (0.45)	$p < 0.001$
Orientation[a]	0.02 (0.1)	0.22 (0.31)	0.86 (0.64)	$p < 0.001$
Judgment and problem-solving[a]	0.02 (0.12)	0.28 (0.34)	0.83 (0.46)	$p < 0.001$
Community affairs[a]	0 (0.04)	0.1 (0.22)	0.72 (0.52)	$p < 0.001$
Home and hobbies[a]	0.01 (0.08)	0.12 (0.27)	0.66 (0.58)	$p < 0.001$
Personal care[a]	0 (0)	0.03 (0.17)	0.38 (0.52)	$p < 0.001$
Global CDR[a]	0.07 (0.17)	0.48 (0.13)	0.78 (0.36)	$p < 0.001$
Cognitive Screening Measure				
MoCA[a]	26.87 (2.51)	22.15 (3.05)	16.57 (5.26)	$p < 0.001$
Functional Assessment				
FAQ (Functional Activities Questionnaire)[a]	0.41 (1.61)	2.04 (3.35)	15.91 (7.7)	$p < 0.001$

Note: Summary statistics treat all variables as continuous measures. CDR scores ranged from 0 to 3 (0 = none; 0.5 = questionable; 1 = mild, 2 = moderate, 3 = severe dementia). FAQ is a questionnaire with total scores that range from 0 to 30.
[a]Indicates differences in demographic characteristic by clinical group $p < 0.05$, and confirmed by post-hoc tests across all pairwise comparisons across groups using Bonferroni correction for multiple comparisons.

TABLE 4 Neuropsychiatric symptoms: Percent of sample reporting each symptom

NPI-Q Symptom	NC($N = 94$)	MCI($N = 91$)	DAT($N = 69$)	*p*-value
NPIQ Delusions (%)[a]	0	1.1	11.6	$p < 0.01$
NPIQ Hallucinations (%)[a]	0	0	10.1	$p < 0.01$
NPIQ Agitation or aggression (%)[a]	2.1	13.2	34.8	$p < 0.01$
NPIQ Depression or dysphoria (%)[a]	7.5	22.2	41.2	$p < 0.01$
NPIQ Anxiety (%)[a]	7.4	20.9	40.3	$p < 0.01$
NPIQ Elation or euphoria (%)[a]	0	1.1	1.5	$p = 0.53$
NPIQ Apathy or indifference (%)[a]	4.3	17.6	43.5	$p < 0.01$
NPIQ Disinhibition (%)[a]	2.1	7.7	24.6	$p < 0.01$
NPIQ Irritability or lability (%)[a]	5.3	16.5	33.8	$p < 0.01$
NPIQ Motor disturbance (%)[a]	0	2.2	20.9	$p < 0.01$
NPIQ Nighttime behaviors (%)[a]	13.3	12.5	28.4	$p = 0.02$
NPIQ Total score (max. 12)[a]	1.05 (2.4)	1.72 (2.63)	4.59 (5.89)	$p < 0.001$
	NC ($N = 95$)	**MCI ($N = 88$)**	**DAT ($N = 57$)**	***p*-value**
Geriatric Depression Scale	1.08 (1.79)	1.59 (2.07)	1.46 (1.76)	$p = 0.18$

Note: Numbers reported for NPIQ symptoms reflect the percent of participants within each clinical group who endorsed having experienced the symptoms within the prior month. Note that the total number of participants varies slightly for each symptom, as some individuals left answers blank. The NPIQ Total reflects the average total number of symptoms experienced by each participant (range 0 to 12).
[a]Indicates differences in demographic characteristic by clinical group at $p < 0.05$, and confirmed by post hoc tests all pairwise comparisons across groups using Bonferroni correction for multiple comparisons.

TABLE 5 Biomarker availability across study groups

Biomarker type	NC	MCI	DAT
Amyloid PET	92 (57%)	12 (8%)	4 (5%)
CSF	34 (21%)	39 (38%)	16 (21%)
Structural MRI	82 (51%)	74 (72%)	44 (58%)
APOE genotype	90 (56%)	90 (87%)	66 (87%)

Note: *n* (%). The proportions are calculated from the total sample size for each of the respective study groups.
APOE: apolipoprotein E; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; PET: positron emission tomography.

participated. In general, a plurality of participants across all study groups had at least one biomarker collected. In addition, structural magnetic resonance imaging (MRI) and *APOE* genotype were available for a subset of participants in all clinical groups. Table 5 includes biomarker availability across study groups.

4 | DISCUSSION

The overall goal of the ARMADA study is to validate the NIHTB in older adults with NC, amnestic mild cognitive impairment (aMCI), and DAT, and to examine other neurologic factors that may be predictive of cognitive status. Here, we presented the demographic and clinical characteristics of one study sample at their initial visit. Briefly, the three study groups (NC, MCI, and DAT) were well matched for most demographic characteristics, with the exception of age and sex. The MCI and DAT clinical groups were slightly older than the NC group. Male individuals made up a smaller proportion of the NC group compared to MCI and DAT cohorts. Characterization of dementia severity levels using CDRs and functional assessment scales differed as expected, with the DAT group demonstrating higher severity compared to the MCI group, and the NC group demonstrating minimal cognitive symptoms. This pattern was also demonstrated by performance on the MoCA, with the AD group scoring the lowest, followed by the MCI and NC groups. In addition, there were differences in informant-reported neuropsychiatric symptoms: individuals in the DAT group had more symptoms than those in the NC and MCI groups. There were no differences in prevalence of reported family history of dementia across groups. Although family history of late-onset AD may be expected to be reported at a higher rate in affected individuals, the counter force may be that cognitively healthy individuals who enroll in studies may do so because of family history. Evaluation of these demographic and clinical characteristics indicate that these study cohorts accurately represent these clinical syndromes for validating the NIHTB across the cognitive aging spectrum.

Future plans for the ARMADA study include comparing performance in all four modules of the NIHTB across cohorts of controls, individuals with aMCI, and individuals with DAT, to determine if the NIHTB will capture differences and discriminate among groups. The relationship between AD biomarkers and NIHTB measures is of great interest. Participants were followed longitudinally, over a two-year period, to track changes in NIHTB performance over time, and we plan to investigate which measures (or combination of measures) are most predictive of future decline. In addition, data were collected for

additional special emphasis groups. Specifically, individuals age 85 and older were recruited to extend the current age-specific norms of the NIHTB. Furthermore, given the need for appropriate and comprehensive norms that better represent ethnic and linguistic diversity, samples of African American participants and Spanish-speaking participants were also followed. A potential future direction of the ARMADA study is to include various dementia subtypes, regardless of etiology.

One limitation of this study to consider is that because of the need to recruit participants from existing cohorts, there may be varying data collection methods and data availability across sites. However, the majority of sites followed a standard protocol and, where possible, the remaining sites conformed to the protocol (e.g., had the same visit windows). Given the proportion of participants with a first-degree family member with cognitive impairment, this sample may be more highly motivated to engage in research, which may somewhat limit generalizability. Another limitation is that the average education level of the three groups is higher than, and therefore not fully representative of, the general population of the United States. Research centers from which the samples were recruited tend to attract individuals who are more likely to volunteer for research, which may coincide with both greater educational attainment and in general, greater accessibility. Future studies with community-based samples may also address the question of the impact of education on our findings. To address disparities in research, there have been calls for increased accessibility so that research participants may more accurately reflect the diversity of the US population, and for standardized instruments for assessing neuropsychological functioning in underserved populations (https://www.nia.nih.gov/report-2019-2020-scientific-advances-prevention-treatment-and-care-dementia/urgent-need-increased). In an effort to address this issue, the ARMADA study had specially recruited special emphasis groups, including cohorts of African American individuals and Spanish-speaking individuals.

Another limitation of the sample is the relatively small number of individuals recruited with DAT. Over recent years, recruitment into the ADRCs and affiliated studies has shifted emphasis from the dementia stage of cognitive aging even earlier to the MCI stage, and even to what is now known as a "preclinical" stage at which individuals are cognitively healthy but have evidence of AD biomarkers. The COVID-19 pandemic, added to the difficulty of studying older adults, especially those with cognitive impairment, and, notably interfered significantly with the planned longitudinal follow-up over two years to assess change over time in all samples. Despite these challenges, ARMADA will provide a comprehensive, cross-sectional, pan-domain study of older individuals across the cognitive aging spectrum, which will support the validation of the NIHTB as a critical assessment tool in the study of cognitive aging as well as numerous additional studies exploring the relation between the NIHTB and other measures of cognitive performance.

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CONFLICT OF INTEREST

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

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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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