






NIA-AA Alzheimer's Disease Framework: Clinical Characterization of Stages

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Background: To operationalize the National Institute on Aging – Alzheimer's Association (NIA-AA) Research Framework for Alzheimer's Disease 6-stage continuum of clinical progression for persons with abnormal amyloid.

Methods: The Mayo Clinic Study of Aging is a population-based longitudinal study of aging and cognitive impairment in Olmsted County, Minnesota. We evaluated persons without dementia having 3 consecutive clinical visits. Measures for cross-sectional categories included objective cognitive impairment (OBJ) and function (FXN). Measures for change included subjective cognitive impairment (SCD), objective cognitive change (Δ OBJ), and new onset of neurobehavioral symptoms (Δ NBS). We calculated frequencies of the stages using different cutoff points and assessed stability of the stages over 15 months.

Results: Among 243 abnormal amyloid participants, the frequencies of the stages varied with age: 66 to 90% were classified as stage 1 at age 50 but at age 80, 24 to 36% were stage 1, 32 to 47% were stage 2, 18 to 27% were stage 3, 1 to 3% were stage 4 to 6, and 3 to 9% were indeterminate. Most stage 2 participants were classified as stage 2 because of abnormal Δ OBJ only (44–59%), whereas 11 to 21% had SCD only, and 9 to 13% had Δ NBS only. Short-term stability varied by stage and OBJ cutoff points but the most notable changes were seen in stage 2 with 38 to 63% remaining stable, 4 to 13% worsening, and 24 to 41% improving (moving to stage 1).

Interpretation: The frequency of the stages varied by age and the precise membership fluctuated by the parameters used to define the stages. The staging framework may require revisions before it can be adopted for clinical trials.

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The recent publication of the National Institute on Aging – Alzheimer's Association (NIA-AA) workgroup proposes 2 clinical staging schemes for the Alzheimer's disease (AD) research framework: (1) the commonly used clinical syndromes of cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia, and (2) a numeric clinical staging scheme of 1 to 6 for individuals who are on the AD spectrum (abnormal amyloid, A+), in which stages 1 to 3 characterize pre-dementia and stages 4

to 6 characterize dementia.¹ The numeric clinical staging scheme incorporates both current cognitive and functional performance as well as cognitive or neurobehavioral decline. The numeric clinical staging scheme was intended to aid in the design of randomized controlled trials, avoid the syndromic labels that can be imprecise when evaluating inclusion criteria and outcomes, and put some structure on the very early stages of subtle clinical changes in CU individuals who did not meet criteria for MCI (ie, stage 2).

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Although these recommendations are appealing, they were proposed as a research framework needing evaluation. We operationalized criteria derived from the Mayo Clinic Study of Aging (MCSA) and evaluated the frequency and stability of the pre-dementia stages (ie, stages 1–3).

Methods

Ascertainment, Enrollment, and Characterization

The MCSA is a longitudinal population-based study of cognitive aging among a stratified random sample of a geographically defined population in Olmsted County, Minnesota^{2,3} that began in 2004. Residents aged 30 to 89 years old are enumerated using the medical records-linkage system of the Rochester Epidemiology Project⁴ and individuals are randomly selected by 10-year age and sex strata, such that men and women are equally represented. Sampling procedures are repeated to maintain approximately 3,000 active participants who are evaluated every

15 months. Because the numeric clinical staging scheme evaluates current performance as well as decline, our analysis used both cross-sectional and longitudinal measures. We included 1,755 participants without dementia age 50 years or older with complete data at 3 consecutive MCSA visits for measures used to define the NIA-AA numeric staging. Visit 3 was considered the index visit for staging individuals and data from this visit were used for cross-sectional measures. Data from visits 1, 2, and 3 were used for longitudinal measures of recent decline.

A clinical diagnosis of CU, MCI, or dementia was determined independently of biomarkers and previous clinical data and diagnoses. Information for each participant was reviewed by a consensus committee composed of physicians, neuropsychologists, and study coordinators.^{2,3} Participants who did not meet established criteria for MCI⁵ or dementia⁶ were deemed CU. Individuals with a diagnosis of dementia were excluded from this analysis.

TABLE 1. Measurements and Cutoff Points Defining Dimensions Used for NIA-AA Numeric Clinical Staging

Cross-sectional	OBJ	Measures: Memory and attention z-score Cutoff points: Normal: (a) both > -1.5 z or (b) both > -2.0 z Abnormal: (a) either ≤ -1.5 z or (b) either ≤ -2.0 z
	FXN	Measure: Functional Activities Questionnaire (FAQ) Cutoff points: None: 0–1 Mild: 2–5 Significant: ≥6
Decline	SCD	Measure: Everyday Cognition (ECog) 12-item assessment ^a Cutoff points: Normal: All ECog questions <3 Abnormal: Any ECog question ≥3 with concern
	ΔOBJ	Measures: Annual decline on memory and attention z-score Cutoff points: Normal: (a) both > -0.1 z/year or (b) both > -0.2 z/year Abnormal: (a) either ≤ -0.1 z/year or (b) either ≤ -0.2 z/year
	ΔNBS	Measures: Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) ^b Cutoff points: Normal: BDI 0–12 and BAI 0–7 Abnormal: BDI ≥13 or BAI ≥8

Operationalization of the clinical staging uses 4 dimensions: objective cognition (OBJ), functional assessment (FXN), subjective cognitive decline (SCD), and neurobehavioral symptoms (NBS). OBJ and FXN are cross-sectional measures and SCD, ΔOBJ, and ΔNBS are measures of recent decline. Sensitivity to cutoff points was evaluated for the OBJ dimension and the alternative cutoff points used are labeled as (a) and (b).

^aThe participant’s ECog assessment was used for individuals without OBJ impairment (ie, stages 1–2), while the participant’s and/or study partner’s ECog assessments were used for individuals with OBJ impairment (ie, stages 3–6).

^bΔNBS was defined as new onset of depression or anxiety on the BDI or BAI. As such, individuals were required to be normal on both measures at the first MCSA visit and abnormal on either at the staging visit (ie, visit 3) to be considered abnormal.

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory-II; ECog = Everyday Cognition (ECog); FAQ = Functional Activities Questionnaire; NIA-AA = National Institute on Aging – Alzheimer’s Association.

All MCSA participants underwent a battery of 9 neuropsychological tests⁷ at each visit. In the current analyses, we focused on memory and attention/executive function domains because they are often the earliest domains to decline in aging and typical AD.⁸⁻¹¹ Memory tests included the Wechsler Memory Scale-Revised (WMS-R) Logical Memory-II (delayed recall), WMS-R Visual Reproduction-II (delayed recall), and Auditory Verbal Learning Test (delayed recall). Attention/executive function tests included Trail Making Test Part B and the Wechsler Adult Intelligent Scale-Revised (WAIS-R) Digit Symbol Substitution Test. Each test was z-scored among CU participants aged 50 years and older who were newly enrolled in the MCSA between 2004 and 2012.¹² Domain z-scores were created by averaging across the 2 or 3 component z-scores and these domain scores were themselves z-scored by calculating a weighted mean and a weighted SD where the weights were based on the age and sex distribution of the Olmsted County population.³

Patient Consent

The MCSA was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants before they joined the study.

Definitions of Clinical Staging Dimensions

Operationalizing the NIA-AA numeric clinical staging scheme involves developing an explicit decision rule to assign individuals to a numeric stage based on data obtained from a battery of clinical and neuropsychological measurements. In a typical research setting, a large number of tests are used and therefore there are essentially an innumerable number of ways to operationalize the staging scheme. For our approach, we grouped the features of the numeric clinical stages along 4 dimensions: objective cognition (OBJ), subjective cognitive decline (SCD), neurobehavioral symptoms (NBS), and functional impact on daily life (FXN). We specified cutoff points for abnormality based on prior work and extensive experience. The definitions of OBJ, SCD, NBS, and FXN are described below and summarized in Table 1.

Objective Cognition

The numeric staging includes 2 components of objective cognition: current cognitive performance (which we define at MCSA visit 3) and decline in cognition (which we define using MCSA visits 1, 2, and 3). We evaluated 2 cutoff points for each component to assess the sensitivity of the staging to variations in the cutoff points.

For current cognitive performance (OBJ), we defined abnormal as a memory or attention/executive z-score of $-1.5 z$ or lower or of $-2.0 z$ or lower. The cutoff point of 1.5 SDs

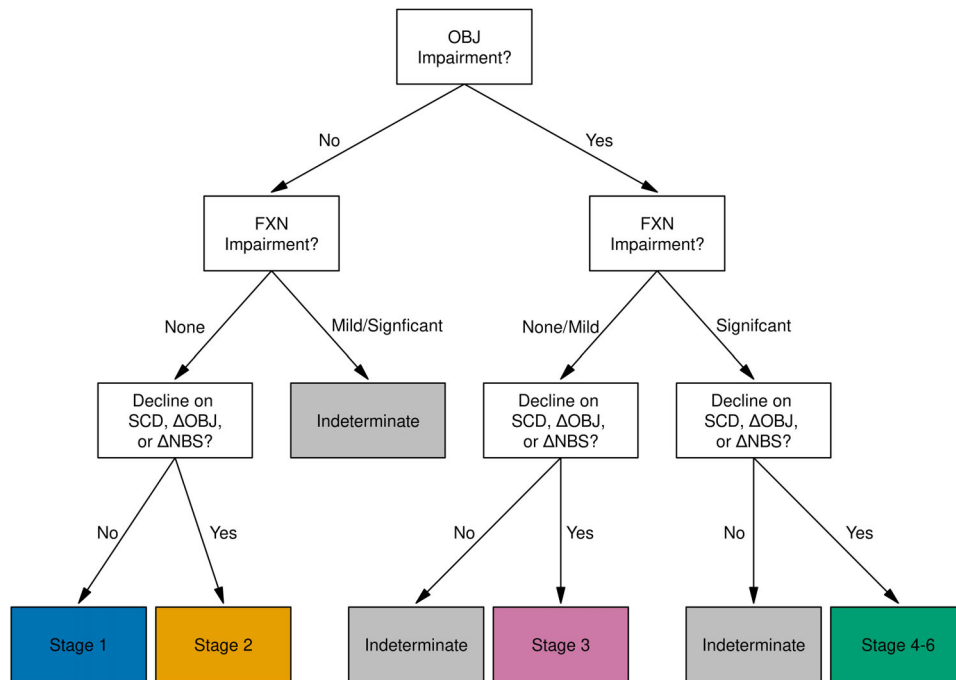


FIGURE 1: Decision tree for determining National Institute on Aging – Alzheimer’s Association (NIA-AA) numeric stage. Flow chart detailing how participants are classified into the 6 numeric stages (or are indeterminate) based on the dimensions defined in Table 1: objective cognition (OBJ), functional assessment (FXN), subjective cognitive decline (SCD), and neurobehavioral symptoms (NBS). OBJ and FXN are cross-sectional measures and SCD, ΔOBJ, and ΔNBS are measures of recent decline.

below the mean is commonly used for defining MCI.^{13,14} The cutoff points we used correspond to the seventh and second percentiles of z-scores in the Olmsted County, Minnesota, CU population. The cutoff point of ≤ -2.0 z indicated more severe impairment than ≤ -1.5 z and resulted in fewer individuals being classified as abnormal on OBJ.

For a decline in cognition (Δ OBJ) measure, we calculated annual decline in memory or attention/executive z-score over three visits (approximately 30 months) by fitting a linear regression within each participant. We used cutoff points of ≤ -0.1 z units/year and ≤ -0.2 z units/year to define abnormal Δ OBJ. These cutoff points were supported by data from the Harvard Aging Brain Study, the Australian Imaging, Biomarker, and Lifestyle Study, and the Alzheimer's Disease Neuroimaging Initiative, in which individuals with abnormal annualized cognitive z-score change — using cutoff points ranging from -0.14 to -0.26 — had an increased risk of MCI.¹⁵ They were also supported by an analysis among 1,913 MCSA CU individuals where any degree of annual decline in memory or attention (ie, ≤ 0 z units/year) was associated with increasing odds of progressing to MCI, with higher odds seen for greater rates of decline (data not shown). The cutoff point of ≤ -0.1 z units/year corresponds to the rate of memory decline in CU at age 85 previously reported¹⁶ and ≤ -0.2 z units/year represents a greater decline in cognition (ie, more impairment) resulting in fewer individuals being classified as abnormal on Δ OBJ.

Subjective Cognitive Decline

For SCD, we used the Everyday Cognition (ECog) 12-Item Assessment, a self-report measure of level of independence in performing cognition-based daily tasks.¹⁷ In a recent MCSA study, van Harten et al demonstrated that individuals who had a consistent SCD (ie, those who had any score on the 12 items ≥ 3) and those with a self-reported concern more rapidly progressed from CU to MCI.¹⁸ Therefore, we defined SCD as a score of ≥ 3 on any of the items on the ECog 12-item test plus a concern. The participant's ECog assessment was used for stages 1 to 2, whereas the participant's and study partner's ECog assessments were used for stages 3 to 6. Although SCD is a decline measure, the ECog questionnaire is designed to assess recent changes over time. Therefore, we used the ECog measures ascertained at visit 3 to define SCD in this study.

Neurobehavioral Symptoms

We used the Beck Depression Inventory-II (BDI) and Beck Anxiety Inventory (BAI) for the neurobehavioral symptom (Δ NBS) dimension.^{19,20} We used the standard cutoff points of ≥ 13 on BDI and ≥ 8 on BAI, which indicate clinical depression or anxiety (ie, mild to severe depression or anxiety). Using these cutoff points, depression and anxiety have been shown to differentiate CU individuals who are likely to progress to MCI in previous work from the MCSA.^{21,22} Because this dimension is

TABLE 2. Participant Characteristics

Characteristic	A+ n = 243	A- n = 449	All n = 1755
Age, years			
Median (IQR)	74 (70, 79)	68 (62, 75)	71 (64, 76)
Min, Max	53, 92	53, 88	52, 92
Men, no. (%)	117 (48%)	255 (57%)	886 (50%)
Education, years, median (IQR)	14 (12, 16)	15 (13, 16)	15 (13, 16)
<i>APOE</i> $\epsilon 4$ carrier, no. (%)	120 (49%)	93 (21%)	507 (29%)
Short Test of Mental Status score, median (IQR)	35 (33, 37)	37 (35, 38)	36 (35, 38)
Clinical diagnosis, no. (%)			
CU	209 (86%)	431 (96%)	1639 (93%)
MCI	34 (14%)	18 (4%)	116 (7%)

Characteristics of MCSA participants with abnormal amyloid (A+), normal amyloid (A-), and all participants regardless of amyloid status. CU = cognitively unimpaired; IQR = interquartile range; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging.

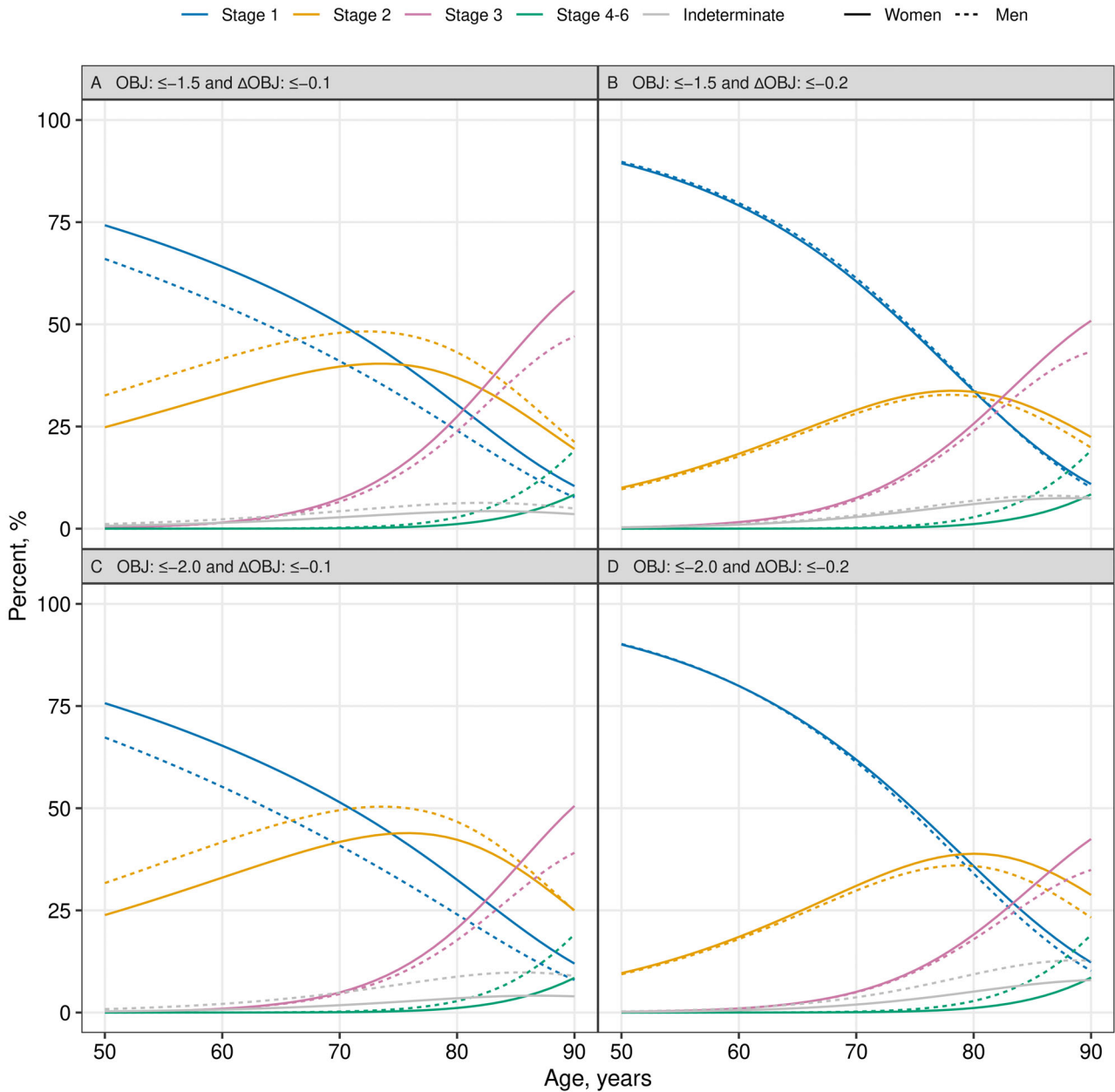


FIGURE 2: National Institute on Aging – Alzheimer’s Association (NIA-AA) numeric stage frequencies by age and sex among A+ participants. Estimated percentage in each NIA-AA numeric stage at each age and by sex for 4 different staging definitions where the cutoff points for the cross-sectional objective criterion (OBJ) and the longitudinal objective criterion (Δ OBJ) are varied. Estimates are from cross-sectional multinomial regression models with stage as the outcome and continuous age and sex as predictors. Solid lines represent the estimates for women and dotted lines represent the estimates for men.

defined as new onset of NBS, we only considered individuals to have abnormal Δ NBS if the person had both BDI <13 and BAI <8 at the beginning of the MCSA (visit 1) and the person had either BDI \geq 13 or BAI \geq 8 at the current visit (visit 3).

Functional Impact on Daily Living

The Functional Activities Questionnaire (FAQ) was used as the primary measure of functional impacts on daily life (FXN).²³ The FAQ includes 10 questions,

which score an individual’s ability to perform activities from 0 (normal) to 3 (dependent) resulting in a total score of 0 to 30 points. Based on prior MCSA data, an FAQ total score >0 occurs in only 13% of non-demented participants,²⁴ although the mean FAQ among CU may be greater than 0.²⁵ Therefore, we used FAQ 0 to 1 to indicate no functional impairment in this study. A score of 6 or greater has been found to separate MCI and dementia, and was used here to indicate significant functional impairment. Scores of 2 to 5 were

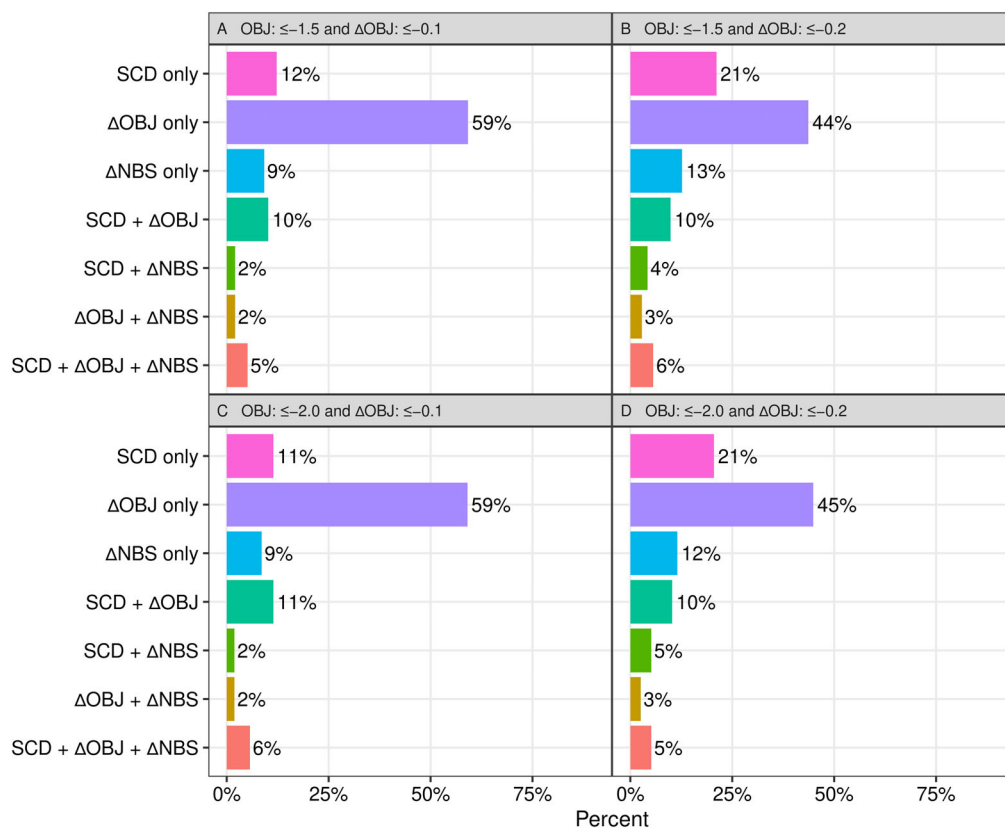


FIGURE 3: Components of the stage 2 definition. Percentage of stage 2 A+ participants with each combination of decline components (subjective cognitive decline [SCD], longitudinal objective cognition criterion [Δ OBJ], and neurobehavioral symptoms [Δ NBS]) for 4 different staging definitions where the cutoff points for the cross-sectional objective criterion (OBJ) and the Δ OBJ are varied. Bars within each panel may not necessarily add to 100% due to rounding.

considered mild impairment.²⁶ The FAQ measure at visit 3 was used for staging.

The decision tree in Figure 1 depicts how the 6 numeric stages were operationalized based on the various cross-sectional and decline dimensions described above. The stages were defined as follows:

Stage 1: Normal OBJ, FXN, SCD (participant), Δ OBJ, and Δ NBS.

Stage 2: Normal OBJ and FXN with at least one of the following abnormal: SCD (participant), Δ OBJ, or Δ NBS.

Stage 3: Abnormal OBJ with no/mild FXN and at least one of the following abnormal: SCD (participant or study partner), Δ OBJ, or Δ NBS.

Stages 4 to 6: Abnormal OBJ and FXN with at least one of the following abnormal: SCD (participant or study partner), Δ OBJ, or Δ NBS.

Individuals with data that do not fit into any of the defined stages are labeled as “indeterminate.”

Amyloid Positron Emission Tomography Imaging

Amyloid positron emission tomography (PET) imaging was used to identify individuals on the Alzheimer spectrum. It was

performed with Pittsburgh Compound B.^{16,27–29} Standardized uptake value ratios (SUVRs) were calculated as the median uptake in a composite region of interest (prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and the precuneus regions)²⁷ normalized by the median uptake in the cerebellar crus gray matter.¹⁶ Since an amyloid PET was not available at each visit, participants were categorized as having abnormal amyloid PET (A+) if they had SUVR ≥ 1.48 at MCSA visit 1, 2, or 3. Participants were classified as A– if they had SUVR < 1.48 at visit 3 or later.

Estimating Frequencies of Stages

Multinomial regression models were fit with the numeric stage as the outcome and continuous age and sex as predictors. From these models, the estimated frequencies (percentages) in each stage at each age and sex were summarized. Likelihood ratio tests were used to test if the staging frequencies differed systematically by sex.

Role of the Funding Source

The funding sources did not influence the design, collection, analysis, interpretation of the data, writing of the report, or the decision to submit for publication.

Results

Because the NIA-AA numeric clinical staging is characterized for individuals on the Alzheimer continuum, our main analysis included 243 A+ participants. Additional analyses were done among 449 A- participants and among 1,755 combined A-, A+, and unknown A status participants. As shown in Table 2, the median age of A+ participants was 74 years (range = 53–92), 52% were women, and the median education was 14 years. The A- participants were younger (median age = 68 years, range = 53–88 years) and 43% were women. Among the overall sample, the median age was 71 (range = 52–92) and 50% were women.

Figure 2 shows the estimated percentage of A+ participants in each stage at different ages by sex for 4 staging definition variations. The 4 variations arise from evaluating combinations of the different OBJ and ΔOBJ cutoff points. The overall patterns of the curves look similar but there are some quantitative differences. Across all definitions, most 50-year-old participants were in stage 1. However, 89 to 90% were in stage 1 using staging definitions with -0.2 z units/year for the ΔOBJ cutoff point (see Fig 2B, D) compared with only 66 to 76% using the cutoff point of -0.1 z units/year (see Fig 2A, C). A larger percentage of 50-year-old participants were in stage 2 using -0.1 z units/year

compared to -0.2 z units/year (24–33% [see Fig 2A, C] vs 9–10% [see Fig 2B, D]). Among the 80-year-old participants, they were more distributed throughout the stages: 24 to 36% stage 1, 32 to 47% stage 2, 18 to 27% stage 3, 1 to 3% stages 4 to 6, and 3 to 9% indeterminate for all definitions. The current study only included persons without dementia, hence the low percentage for stages 4 to 6. There were no significant differences in the percent of individuals within each stage by sex.

Stage 2 was the most challenging to define as participants were required to have normal OBJ and FXN at visit 3 but be abnormal on at least 1 of 3 decline measures (SCD, ΔOBJ, or ΔNBS). Most stage 2 A+ participants had only 1 abnormal decline measure across the 4 staging definition variations (78–80%), whereas 14 to 18% had 2, and 5 to 6% were abnormal on all 3 (Fig 3). The most common reason for inclusion in stage 2 was having abnormal ΔOBJ only (44–59%), whereas 11 to 21% had SCD only, and 9 to 13% had ΔNBS only. Because the ΔOBJ cutoff point of -0.1 z units/year required less of a decline in cognition for classification as abnormal ΔOBJ, more participants were classified as stage 2 by ΔOBJ only when using this cutoff point (see Fig 3A, C). In contrast, using the ΔOBJ cutoff point of -0.2 z units/year led to more participants classified by SCD only or ΔNBS only (see Fig 3B, D).

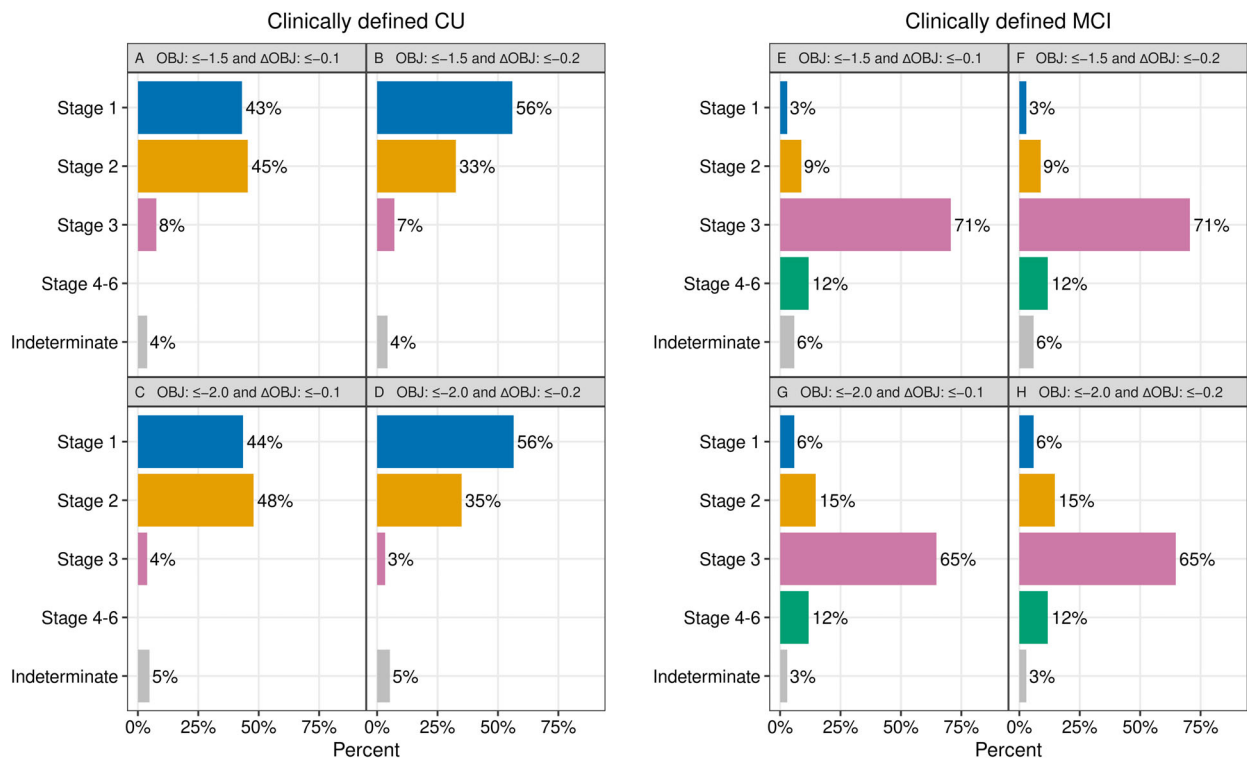


FIGURE 4: Comparison of the numeric clinical staging and clinically defined diagnosis. Percentage of clinically defined cognitively unimpaired (CU) and mild cognitive impairment (MCI) A+ participants in each numeric clinical stage for 4 different staging definitions where the cutoff points for the cross-sectional objective criterion (OBJ) and the longitudinal objective criterion (ΔOBJ) are varied. Bars within each panel may not necessarily add to 100% due to rounding.

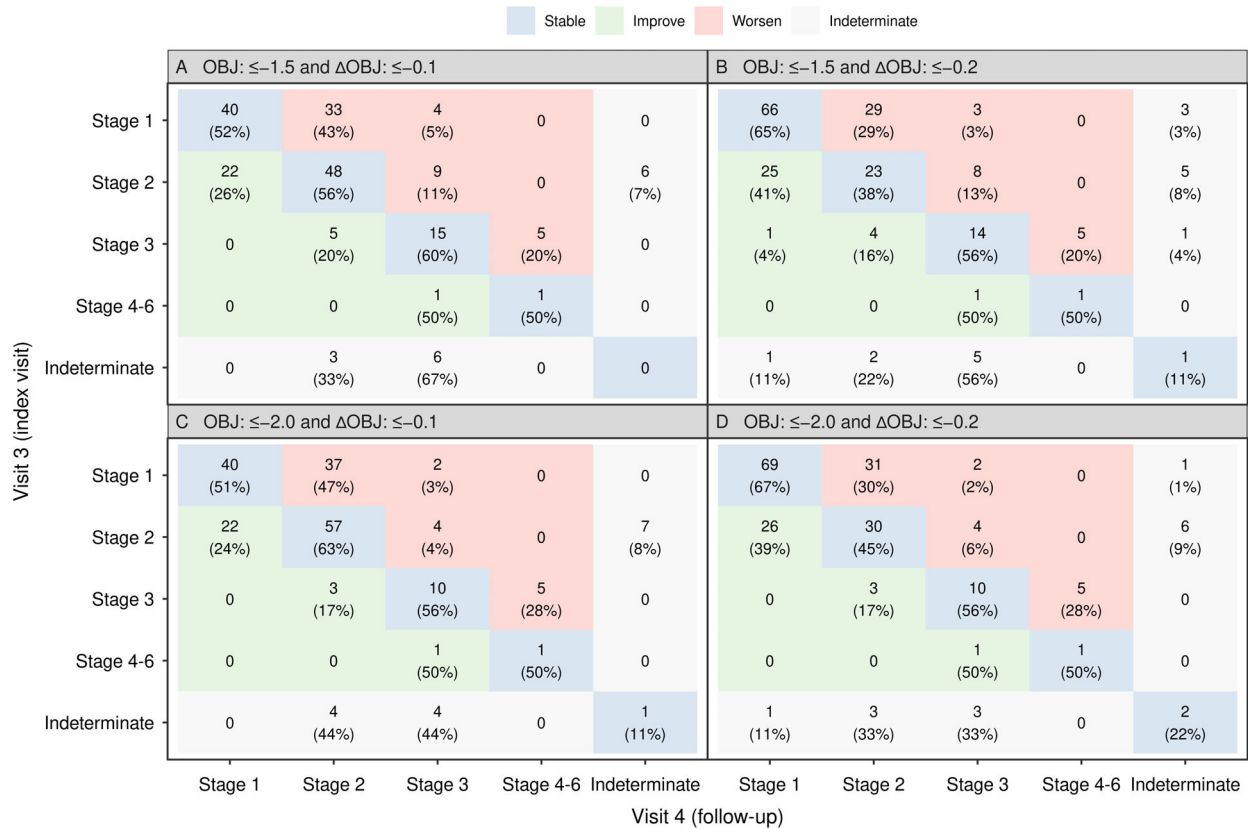


FIGURE 5: Stability of staging definitions. Percentage of participants that stayed in the same stage (stable; blue), moved to a lower stage (improve; green), moved to a higher stage (worsen; red), or were indeterminate (grey) between visits 3 and 4 (approximately 15 months) among 198 A+ participants with follow-up. Percentages are shown for 4 different staging definitions where the cutoff points for the cross-sectional objective criterion (OBJ) and the longitudinal objective criterion (ΔOBJ) are varied. Stage at visit 4 (follow-up) was defined in the same way as stage at visit 3 but used visit 4 for the cross-sectional measures (index visit) and visits 2, 3, and 4 for the decline measures. Row percentages may not necessarily add to 100% due to rounding.

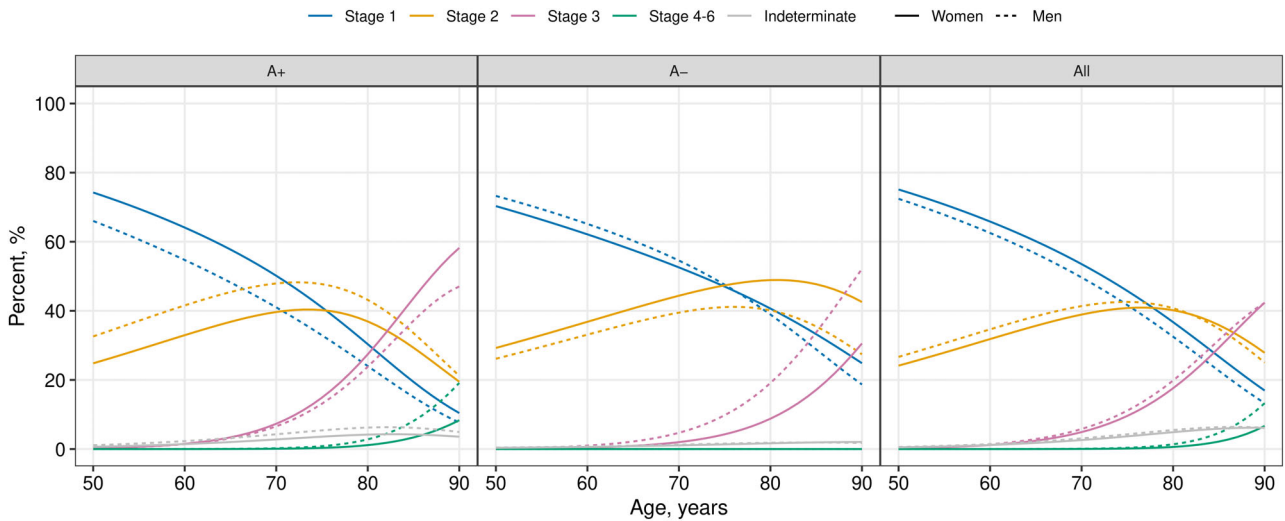


FIGURE 6: National Institute on Aging – Alzheimer’s Association (NIA-AA) numeric stage frequencies by age and sex among A+ participants, A- participants, and all participants. Sensitivity analysis showing the estimated percentage in each NIA-AA numeric stage at each age and by sex among A+ participants, A- participants, and among all participants using the staging definition where the cutoff point for the cross-sectional objective criterion was $OBJ \leq -1.5$ and the cutoff point for the longitudinal objective criterion was $\Delta OBJ \leq -0.1$. Estimates are from cross-sectional multinomial regression models with stage as the outcome and continuous age and sex as predictors. Solid lines represent the estimates for women and dotted lines represent the estimates for men.

The number of individuals who did not fit into one of the stages (ie, indeterminate) was small (10–12 individuals or 4–5%). The majority of the indeterminate individuals had normal OBJ but mild or impaired FXN (64–82%), whereas a smaller number had abnormal OBJ but were normal on all SCD, Δ OBJ, and Δ NBS decline measures (18–36%).

Figure 4 shows the percent of A+ participants in each stage for the 4 staging definition variations for either clinically defined CU or MCI participants. Among CU, most participants were in stages 1 or 2 (88–92%) but the proportion in stage 1 versus stage 2 depended on the choice of the cutoff point for Δ OBJ. Similar numbers were in each (43–44% stage 1 vs 45–48% stage 2) using the cutoff point of -0.1 z units/year (see Fig 4A, C), whereas 56% were in stage 1 and 33 to 35% were in stage 2 using -0.2 z units/year (see Fig 4B, D). Only 3 to 8% of CU participants were in stage 3, none in stages 4 to 6, and 4 to 5% were indeterminate. Among MCI participants, most were in stage 3 (71% when $\text{OBJ} \leq -1.5$ z units [see Fig 4E, F], 65% when $\text{OBJ} \leq -2.0$ z units [see Fig 4G, H]), with roughly equal numbers in stage 2 (9–15%) and stages 4 to 6 (12%). A small number were in stage 1 (3–6%) or indeterminate (3–6%).

Stability

To assess stability of the staging definitions, we compared the stage at visit 3 to the stage at visit 4 (approximately 15 months later) among 198 of 243 (81%) A+ participants with follow-up data (Fig 5). Stability differed across the stages and 4 staging definition variations. Among individuals in stage 1 at visit 3 (see Fig 4, top row in each panel), at visit 4, 51 to 67% remained in stage 1 (stable), 32 to 50% moved to a higher stage (worsened), and a small percent (0–3%) were indeterminate at visit 4. Among individuals in stage 2 (see Fig 4, second row in each panel), 38 to 63% remained stable, 4 to 13% worsened, 24 to 41% improved (moved to stage 1), and 7 to 9% were indeterminate at visit 4. More improved with the Δ OBJ cutoff point of -0.2 z/year (see Fig 4B, D) compared to -0.1 z/year (see Fig 4A, C). Among stage 3 individuals (see Fig 4, third row in each panel), 56 to 60% were stable, 20 to 28% worsened, 17 to 20% improved, and 0 to 4% were indeterminate at visit 4.

Applying the NIA-AA Staging Scheme to A– and all Individuals

Although the NIA-AA staging scheme was designed for A+ participants, we also used our entire cohort and the subset of A– persons to further explore the utility of the scheme. Figure 6 shows the percent of 243 A+ participants, 449 A– participants, and all 1,755 participants that

fall in each stage by age and sex using the staging definition of $\text{OBJ} \leq -1.5$ z and $\Delta\text{OBJ} \leq -0.1$ z/year. Although the curves showed some variability, they were not dramatically different from those in the A+ participants.

Discussion

The numeric clinical staging scheme proposed by the NIA-AA research framework for AD was designed to facilitate clinical characterization of A+ participants in randomized controlled trials for AD. When these criteria were applied to a population-based sample of A+ individuals, focusing on stages 1 to 3, we found that the population without dementia could be classified using various implementation strategies for these criteria with some reservations.

Age constituted a major factor in determining the frequencies of the stages. As would be expected, most A+ 50-year-old individuals were stage 1, whereas among A+ 80-year-old individuals, only 24 to 36% of the population was stage 1 with corresponding increases in stages 2 and higher. This parallels the incidence of mild cognitive impairment and dementia with age.¹⁴

The frequencies of stages 1 to 3 were clearly influenced by the implementation of the criteria used to define the stages. Changing the threshold used for defining cognitive impairment (OBJ) to classify individuals with more severe impairment (-2.0 z) as abnormal resulted in an increased percentage in stage 2 and a decreased percentage in stage 3, as would be expected. Using the -0.2 z units/year cutoff point for Δ OBJ resulted in a decreased percentage in stage 2 and a corresponding increase in stage 1 compared to -0.1 z units/year. Although these cutoff points may appear relatively lenient, our prior work has demonstrated that practice effects significantly impact performance trajectories and that trajectories vary by biomarker profile.^{7,30} Papp et al found an increased risk of MCI among individuals with subtle cognitive decline using tertile cutoff points for annualized cognitive change ranging from -0.14 to -0.26 in their data. Those results indicate that small declines in cognition, similar to declines examined in this study, can be meaningful.¹⁵

When assessing which of the 3 criteria, SCD, Δ OBJ, or Δ NBS, contributed the most to qualifying for stage 2, Δ OBJ was the leading factor. SCD was the second qualifying measure, with Δ NBS being third. Although Δ OBJ was the leading factor in qualifying for stage 2, the percentage of individuals in stage 2 with Δ OBJ only did vary with different cutoff points. Few individuals were classified as stage 2 based on Δ NBS only. However, the implementation of the criteria for Δ NBS

required a normal BDI and BAI at visit 1 and a change in either by visit 3; in this population-based sample, incident depression and incident anxiety were not common. This may have compromised the utility of this measure. These data suggest that Δ NBS may not be a useful element by which to classify individuals on the AD spectrum and raise questions about the appropriateness of this measure in the AD framework. In addition, NBS, such as depression, may actually improve over time making it a less reliable feature of AD.³¹

We compared the classifications of individuals in the stages to our clinical diagnoses of CU, MCI, and dementia. In general, our CU diagnosis corresponded to stages 1 and 2 and MCI to stage 3. Within MCI, the frequency of stage 3 varied from 65 to 71% and from 15 to 9% for stage 2 depending on the OBJ cutoff point used (≤ -2.0 z vs ≤ -1.5 z). Although we expect these 2 classifications to be similar, it is not surprising that there is not perfect agreement. The published criteria for MCI⁵ do not require a certain degree of cognitive impairment but rather a change in cognition only. Therefore, MCI individuals could be classified as stage 2 because stage 3, as defined in the framework, does require a degree of cognitive impairment in addition to a change in cognition.

The proposal to develop stages for the AD continuum was intended to improve the current classification of clinical syndromes, such as CU, MCI, and dementia. The concern about the cognitive syndromes pertains to their lack of specificity and the boundaries between the conditions.³² It is well recognized that these entities exist along a cognitive continuum, but the fractionation into clinical syndromes is useful for both clinical practice and research. A recent evidence-based medicine review of over 11,500 publications on MCI documented that the construct is useful, its prevalence is high (15–20% of the population 70 years and older), and that progression to dementia is predictable within boundaries.¹⁴ In addition, the clinical acceptance in the United States and Europe is high.^{33,34} However, there are problems with the lack of precision of the diagnostic boundaries; hence alternative characterizations have been sought.³⁵

The numeric clinical staging scheme proposed in the NIA-AA research framework attempts to circumvent some of these concerns by giving the stages a numerical label. However, many of the fundamental issues persist (eg, boundaries between stages 1 and 2, and between stages 2 and 3). The present study assessed some of these issues with data from a longitudinal population-based study of aging and cognition, the MCSA. The frequencies of stages 2 and higher increase with age and there are some transitions between the stages in expected directions. However,

there is uncertainty in the boundaries between the stages, which is most notably demonstrated in the most nuanced category of stage 2. Stage 2 is meant to capture individuals in the range of “unimpaired” cognition who may be transitioning toward impairment (ie, individuals with the earliest detectable clinical evidence of symptoms attributable to Alzheimer continuum pathology). However, given the numerous ways to capture stage 2, most of which depend on longitudinal data, a standardized characterization will be challenging. Choosing different cognitive measures or abnormal thresholds would affect the classification of individuals in this stage. We found most stage 1 individuals were stable or worsened (ie, moved to a higher stage) and most stage 2 individuals were stable or improved (ie, moved to stage 1) at the next visit. However, using different Δ OBJ cutoff points affected the stability; the Δ OBJ cutoff point of ≤ -0.2 z/year resulted in more stable and fewer worsening for stage 1 and fewer stable and more improving for stage 2. The nontrivial reversion plus indeterminate proportions of the A+ participants suggests that more work needs to be done in refining the variables used to define the numeric stages.

The construct of SCD is also challenging but recent research is shedding light on this issue.^{36,37} Because many factors affect SCD, it is probably best when combined with an objective measure of performance. Finally, the Δ NBS measure may be the most challenging. Studies have shown the emergence of subtle psychiatric symptoms in evolving cognitive impairment, yet developing a reliable metric for Δ NBS can be difficult.^{38,39} This problem is further complicated by wide use of antidepressants and anxiolytics among elderly persons with access to primary health care. The framework might consider eliminating the Δ NBS category in characterizing individuals on the AD spectrum for clinical trial purposes.

This study represents one of the first attempts to fit data into the numeric clinical staging proposed by the NIA-AA research framework. The devil is in the details when trying to be more specific with respect to the precise definitions and some of the challenges in implementing this strategy are highlighted. Although the staging works to a degree — you can classify participants into the stages with few indeterminates — it is not easy to implement given the number of decisions underlying operationalization (ie, which assessments and cutoff points to use) and it is not clearly an improvement over the clinical syndromes given the nontrivial reversion rates in stage 2. The AD framework should be modified to account for the lack of contribution by Δ NBS and the relative instability of stages, particularly stage 2, with respect to longitudinal outcomes, and the framework will need to be evaluated in other populations to assess generalizability.

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Author Contributions

R.C.P., H.J.W., S.D.W., and C.R.J. contributed to conception and design of the study. R.C.P., H.J.W., S.D.W., W.K.K., M.M.Ma., T.M.T., and C.R.J. contributed to acquisition and analysis of data. R.C.P., H.J.W., S.D.W., J.A.F., Y.E.G., J.G.-R., D.S.K., W.K.K., V.L., M.M.Ma., M.M.Mi., N.H.S., T.M.T., P.V., and C.R.J. drafted a significant portion of the manuscript or figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Data from the MCSA, including data from this study, are available upon request.

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