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An initial empirical operationalization of the earliest stages of the Alzheimer's Continuum

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Abstract

Purpose: The Alzheimer's Continuum (AC) includes 2 preclinical stages defined by subjective cognitive complaints, transitional cognitive declines, and neurobehavioral symptoms. Operationalization of these stages is necessary for them to be applied in research.

Methods: Cognitively normal individuals with known amyloid biomarker status were selected from the National Alzheimer's Coordinating Center Uniform Data Set. Participants and their caregivers provided information on subjective cognitive complaints, neurobehavioral features, and objective cognitive functioning.

Patients: The sample included 101 amyloid positive (A+) and 447 amyloid negative (A−) individuals.

Results: Rates of subjective cognitive complaints (A+: 34.90%, A−: 29.90%) and neurobehavioral symptoms (A+: 22.40%, A−: 22.40%) did not significantly differ between A+/− individuals. However, the frequency of transitional cognitive decline was significantly higher among A+ (38.00%) than A− participants (24.90%). We explored various empirical definitions for defining the early stages of the AC among A+ participants. Rates of classification into AC stage 1 vs. AC Stage 2 varied depending on the number of symptoms required: 57.40% vs. 42.60% (1 symptom), 28.70% vs. 71.30% (2 symptoms), and 6.90% vs. 93.10% (all 3 symptoms).

Conclusion: The presence of 2 of the proposed symptom classes to separate AC stage 2 from stage 1 seems to provide a good empirical balance.

Keywords

Alzheimer's; subjective cognitive complaints; neurobehavioral symptoms; transitional cognitive decline; multivariate base rate; neuropsychological tests

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Introduction

In recognition of the distinction between the pathological Alzheimer's disease process and its phenotypic manifestations, the National Institute on Aging and Alzheimer's Association (NIA−AA) released a new research framework defining the Alzheimer's Continuum (AC) by the presence of at least 1 positive β-amyloid biomarker,[1] (indicated by A +/− for the presence/absence of biomarker evidence), independent of clinical symptoms. Nevertheless, the AC is broken down into 6 severity stages based on clinical symptoms. The latter 4 stages map onto familiar clinical syndromes for mild cognitive impairment and mild, moderate, and severe dementia, respectively. AC stages 1 and 2, though, represent less well characterized preclinical stages, defined by the absence (stage 1) or presence (stage 2) of three types of symptoms: 1) subjective cognitive complaints (from the perspective of patient, provider, and/or collateral), 2) "transitional cognitive decline", and 3) neurobehavioral changes. There are important measurement questions regarding each of these symptom classes that have yet to be addressed in research.

Subjective cognitive complaints and neurobehavioral symptoms

Under the proposed framework, subjective cognitive complaints and neurobehavioral symptoms can be noted by the patient, a collateral informant, or a healthcare provider. Subjective cognitive complaints of patients tend to be associated with greater amyloid burden and more rapid functional declines.[2, 3] Similarly, psychiatric symptoms can be early manifestations of the underlying Alzheimer's disease process.[4] However, the level of agreement across symptom raters has yet to be established, and the relative prevalence of these symptoms in A+/− individuals remains unclear. Thus, more research is needed to ascertain consistency in symptom reports across raters and examine the degree to which the presence/absence of different symptom classes impacts AC staging.

Transitional cognitive decline

Transitional cognitive decline is defined by reductions in cognitive test performance without frank impairment either at a single evaluation or via serial evaluations.[1] Because clinical trial designers would not typically have access to longitudinal cognitive testing at the time of enrolling participants, methods for determining whether someone may be experiencing transitional cognitive decline based on a single evaluation time point are necessary for staging participants at baseline.

Prior research suggests that an effective means of defining transitional cognitive decline at a baseline evaluation is to use a multivariate base rate approach.[5–7] Multivariate base rate techniques evaluate the frequency of low scores obtained from a neuropsychological test battery after taking into account demographic factors.[8–10] With this methodology, the presence of a unusually weak, but unimpaired, neuropsychological profiles can define transitional cognitive decline even in the absence of serial evaluation. To date, though, researchers have not compared rates of transitional cognitive decline using multivariate base across amyloid positive and negative groups. Moreover, the relative contribution of objective cognitive measures versus self-reported data to AC staging has not been assessed. Therefore, research is needed to examine differences in transitional cognitive decline (defined by a

multivariate base rate approach) between A+ and A− groups and assess the importance of transitional cognitive decline to AC staging.

Integration of symptom types for early AC classification

Most importantly, researchers have not investigated how the varying combinations of symptom presentations will impact classification of amyloid positive, but cognitively unimpaired, individuals into AC stages 1 and 2. For example, we currently do not know how common it is to be amyloid positive with 1, 2, or 3 of the symptom classes. Such considerations are critical for clinical trial design, which requires estimates of the percentage of individuals within a given population that will meet certain criteria, such that adequate numbers of participants can be recruited to detect a given effect.

Current study

In light of these factors, the current study had three goals:

1. to evaluate the frequency and inter-observer agreement for subjective cognitive complaints and neurobehavioral symptoms among cognitively normal A+/A− individuals;
2. to examine differences in the prevalence of transitional cognitive decline, as operationalized by multivariate base rate abnormalities, between A+ and A− groups; and
3. to present information on how different symptom combinations impact the rate of classification of A+ participants into AC stage 1 versus AC stage 2.

Methods

Sample

We requested all available Uniform Data Set (UDS) data on 1/29/19, which included 39,412 participants from 39 Alzheimer's Disease Research Centers. Data collection occurred under the auspices of the respective institutions' IRBs. Our local IRB reviewed the project and determined it was exempt from further review, as the data was de-identified.

Of the original participants, we omitted those who were lacking amyloid biomarker data, leaving 2,140 individuals for consideration. Next, because the current study focused on AC stages 1 and 2, in which individuals do not demonstrate overt cognitive impairment, the sample was limited to those with a Clinical Dementia Rating (CDR) Dementia Staging Instrument ® score of 0.[11–13] Finally, because the neuropsychological tests in the UDS 3.0 neuropsychological battery (UDS3NB) often require proficiency in the English language, the sample was further limited to those with English as their primary language, leaving a final sample of 548 individuals. Demographic characteristics of this sample are provided in Table 1 by amyloid status.

Measures

Amyloid status.—PET-amyloid imaging and CSF data are collected at a subset of Alzheimer's Disease Research Centers and are included in the UDS at the discretion of the

individual sites. Data are collected using individualized protocols for the member sites with local standards for positivity, such that methods of evaluation and cutoffs may vary by Center (see Supplemental Table 1). Individuals were coded as A+ if they had at least 1 positive amyloid biomarker as defined by the Center in question. In contrast, individuals were coded as A− if all available biomarkers were negative.

Subjective cognitive problems.—The presence of subjective cognitive complaints was assessed in a categorical format by Alzheimer's Disease Research Center clinicians at interview. The patient and caregiver were both asked to report on whether they felt the patient demonstrated a decline from baseline cognitive functioning. Similarly, the examiner provided a rating of the presence of cognitive impairment based on his/her own clinical judgment. For example, clinicians responded yes or no to the following question: "Based on the clinician's judgment, is the subject currently experiencing meaningful impairment in cognition?".

Neurobehavioral variables.—Jack and colleagues[1] provided 3 examples of neurobehavioral symptoms that might result from the pathological changes associated with Alzheimer's disease; namely, depression, anxiety, and apathy. These variables are indexed in the UDS in 3 ways. First, the clinician provides a rating of the presence of each aforementioned variable based on his/her clinical judgment. Second, the caregiver completes the Neuropsychiatric Inventory Questionnaire (NPI-Q),[14, 15] regarding his/her observations of neurobehavioral symptoms exhibited by the patient. Third, the patient reports on depressive symptoms on the Geriatric Depression Scale-Short Form (GDS).[16–18] Individuals were categorized as having clinically significant self-reported depression if their summed score on the GDS was ≥5.[19]

Cognitive variables.—The measures in the UDS3NB have been described in detail elsewhere.[20, 21] Briefly, they include 1) the Benson Figure, which contains a copy portion and a delayed recall portion;[22] 2) the Craft Story,[23] a measure of learning and memory for an orally presented story (verbatim recall used in the current study); 3) the Multilingual Naming Test (MINT), a confrontation naming task;[24] 4) Number Span Forwards and Backwards (total score used for the current study); 5) Trailmaking Test parts A and B, which assess number sequencing and letter-number sequencing, respectively; and 6) semantic (animals and vegetables) and letter fluency (F- and L-words) tasks.

Analyses

Subjective cognitive problems and amyloid status.—Interrater agreement of subjective cognitive problem reports across clinicians, caregivers, and patients was assessed using Fleiss' Kappa. Values were interpreted via rules of thumb put forth by Cohen for poor (.01–.20), fair (.21–.40), moderate (.41–.60), substantial (.61–.80), and almost perfect (.81–1.00) agreement.[25] Differences in the frequency of subjective cognitive complaints by amyloid status were assessed via chi-square tests.

Neurobehavioral symptoms and amyloid status.—We next examined rates of reported neurobehavioral symptoms by amyloid status, as endorsed by the clinician,

caregiver, and patient. Level of agreement across these raters was assessed using Fleiss' Kappa for variables with more than two raters (i.e., depression) and Cohen's Kappa for variables with two raters (i.e., anxiety and apathy). Next, chi-square tests of independence were conducted to assess for differences in the frequency of each neurobehavioral symptom by amyloid status.

Cognitive performance and amyloid status.—Standardized, demographically-adjusted cognitive scores were created using data from confirmed clinically normal (CDR = 0), A− status participants (n = 447). Raw cognitive scores were corrected for age, sex, and education, then standardized using a regression-based approach following the methods outlined by Weintraub and colleagues.[20] Results of regressions are provided in Supplemental Table 2. This step yielded a set of normative z-score values for each cognitive test, which were utilized for analysis. We tested differences across A+/A− individuals in cognitive test performance using independent samples t-tests. Cohen's d was used as the measure of effect size for these comparisons with interpretation of small (.2), medium (.5), and large (.8) effects according to established rules of thumb.[26]

Next, we examined whether A+/A− groups differed in their likelihood of demonstrating transitional cognitive declines, as defined by a multivariate base approach. Multivariate base rate techniques assess the number of low scores that should be expected across a test battery after accounting for demographic factors.[8–10] This method allows for identification patterns of low, but not grossly impaired, scores that suggest the presence of transitional cognitive decline. Prior research with the UDS 3.0 battery suggests that having at least 2 low demographically adjusted z-scores ≤ −1.34 (i.e., at or below the 9th percentile) provides the best balance between sensitivity and specificity for differentiating those who convert to mild cognitive impairment from those who remain cognitively normal (see Supplemental Table 3, adapted from Kiselica and colleagues).[6] Consequently, participants with 2 or more low scores at or below the 9th percentile on the UDS3NB were coded as positive for transitional cognitive decline. We tested for a difference in the rate of transitional cognitive decline between A+ and A− groups using a chi-square test of independence.

Impact of symptom combinations and AC stages 1 and 2.—Finally, we examined the extent to which different symptom combinations impact the rate of classification of A+ individuals into AC stages 1 and 2. Based on the definition of AC stage 2 put forth in the NIA−AA framework,[1] we operationalized the three symptom classes as follows:

- a subjective cognitive complaint by the clinician, caregiver, or patient;
- a neurobehavioral symptom reported by the clinician, caregiver, or patient;
- transitional cognitive decline, defined as having at least 2 demographically adjusted scores on the UDS3NB at or below the 9th percentile.

We applied these 3 criteria in amyloid positive individuals to define AC stage 2 using lax (at least 1 symptom class present), moderate (at least two symptom classes present), or strict (three symptom classes present) standards. Under this framework, stage 1 was defined as the converse of stage 2; that is, those who failed to meet the standard for stage 2 were considered to be in stage 1.

Results

Subjective cognitive problems and amyloid status

Rates of clinician, caregiver, and patient reported subjective cognitive problems are presented in Table 2. Findings were suggestive of fair agreement ($\kappa = .24$) amongst reporters. There were no significant differences in the rate of subjective cognitive complaints across amyloid groups.

Neurobehavioral symptoms and amyloid status

Prevalence of neurobehavioral symptoms by rater and amyloid status are provided in Table 2. Interrater agreement for neurobehavioral symptoms was fair for depression ($\kappa = .34$) and moderate for anxiety ($\kappa = .52$) and apathy ($\kappa = .53$). Tests of amyloid group differences in rates of neurobehavioral symptoms were not significant, with the exception of caregiver-reported depression being more common in the A− group.

Cognitive performance and amyloid status

Results of independent samples t-tests for cognitive scores are summarized in Table 3. Most group differences were non-significant. However, A+ individuals performed more poorly on number span and trailmaking tasks, with effect sizes in the small range. The rate of transitional cognitive decline was significantly higher in the A+ (38.00%) than the A− group (24.90%), $\chi^2(1) = 6.98$, $p = .008$.

Impact of symptom combinations on defining AC stages 1 and 2

We examined how the number of symptom classes used to define AC stages 1 and 2 impacted rates of classification among A+ individuals (see Table 4 for a summary of results). When only 1 symptom needed to be present, a fairly even distribution of individuals met the standard for AC stages 1 and 2. When 2 symptom classes were required, however, the rate of individuals diagnosed as AC stage 2 dropped to about a quarter. Finally, when having all 3 symptom classes was necessary, very few participants met the standard for AC stage 2, such that more than 90% of individuals would be labeled as stage 1.

Discussion

In the current study, we sought to better understand core criteria for defining AC levels 1 and 2. Specifically, we analyzed the rates of subjective cognitive complaints, neurobehavioral symptoms, and transitional cognitive decline in individuals defined as A+/−. We also assessed agreement among raters for reports of cognitive complaints and neurobehavioral symptoms. Finally, we report on the impact of varying diagnostic standards for categorizing A+ individuals into AC stages 1 and 2.

Subjective cognitive problems and amyloid status

We found only fair agreement across raters (self, caregiver, and clinician) for subjective cognitive complaints in non-impaired A+ individuals. This finding stands in contrast to a previous study that described moderate agreement in reported cognitive symptoms between patients and caregivers.[27] To our knowledge, the present study is the first to report on

agreement in subjective ratings of cognition across clinicians, patients, and caregivers in an A+ sample. Our results suggest further work is necessary to identify methods to increase agreement among raters. Alternatively, it may be necessary to weight the ratings of different reporters by their relative importance for prognosis. Indeed, recent research suggests that patient and study partner reports provide account for unique variance when predicting clinical progression.[28]

Regarding amyloid status, there were no significant differences in the rate of subjective cognitive complaints between A+ and A− individuals. A prior study, however, indicated that A+ participants reported significantly more subjective memory complaints than A− participants.[29] The outcome used in this study was a continuous questionnaire measure, in contrast to our dichotomous interview item. Thus, use of a yes/no question format may obfuscate subtle differences in self- or observer-reports of cognition between A+ and A− groups.

Neurobehavioral symptoms and amyloid status

We found that interrater agreement for neurobehavioral symptoms was only fair for depression but moderate for anxiety and apathy, similar to results from prior studies.[30, 31] Having at least one reporter endorse a neurobehavioral symptom occurred at the same rate among A+ and A− individuals. While these symptoms occur at similar rates in A+ and A− individuals, they may be interpreted differently in these groups. Indeed, Johansson and colleagues found that anxiety interacts with amyloid to predict future cognitive decline, such that anxiety may be a harbinger of clinical progression in A+ but not A− groups.[4]

Cognitive performance and amyloid status

Most group differences on cognitive scores between A+ and A− participants were non-significant, though there were mildly weaker performances by A+ individuals on tasks involving attention, processing speed, and executive functioning (i.e., the number span and trailmaking tasks). Alzheimer's has long been associated with memory impairment,[32] and previous metA−analytic results suggest that amyloid burden is mainly correlated with episodic memory performance among cognitively healthy adults.[33] However, the notion that memory dysfunction is the sole defining feature of early Alzheimer's has been challenged, with many arguing that executive dysfunction can be prominent as well,[34–36] and our findings support this suggestion.

While both groups were, by definition, cognitively unimpaired (mean level cognitive performances were similar between groups), our analyses revealed that transitional cognitive decline, as defined by a multivariate base rate approach, occurred about 13% more often in individuals who were A+ than those who were A−. Results conform with previous research, [37] which suggests that early amyloid deposition is a risk factor for subtle abnormalities in cognitive performance that do not rise to the level of gross impairment. Further, they suggest that the multivariate base rate approach holds promise for operationalizing transitional cognitive decline when only data from a single cognitive evaluation are available.

Impact of symptom combinations on defining AC stages 1 and 2

We assessed the degree to which classification of individuals into AC stages 1 and 2 would differ, depending on the number of symptom classes (i.e., subjective cognitive complaints, transitional cognitive decline, and neurobehavioral changes) required for a stage 2 diagnosis. There was a fairly equal dispersion of individuals diagnosed as AC stage 1 and 2 when only 1 symptom class was required for an AC stage 2 diagnosis. However, the rate of those categorized as AC stage 2 decreased substantially when 2 symptom classes were required, dropping to approximately one quarter. Finally, few individuals met standards for stage 2 when all 3 symptom classes were necessary for a stage 2 diagnosis (~7%).

Thus, the ultimate empirical definitions of AC stages 1 and 2 will depend on the preferences of the clinical and research communities. If there is a need to avoid false positives and limit anxiety in otherwise healthy patients, the strict standard (presence of all 3 symptom classes) may be preferred. On the other hand, if there is a desire to reduce false negatives and limit under diagnosis, the lax standard (presence of at least 1 symptom class) may be preferred. The moderate standard (presence of at least 2 symptom classes) represents a good balance between these poles. It identifies a reasonable number (about 25%) of individuals as stage 2 for purposes of clinical trial selection and longitudinal analysis, while avoiding over pathologizing patients. Thus, we advocate for use of the moderate standard for future research, though further studies on classification accuracy are needed.

Limitations

These results are considered in the context of some limitations. First, the UDS sample is composed mainly of highly educated, white individuals, such that this sample may not be representative of the broader population. Future studies would benefit from the inclusion of individuals from more varied demographic backgrounds. Second, lack of uniformity in the assessment of amyloid status was present due to the fact that individualized protocols were used at the various Alzheimer's Disease Research Centers. Thus, it will be important to more specifically define the methods and criteria utilized to determine amyloid biomarker positivity in the future. Third, although interpreting this data in a cross-sectional design more closely mimics methods utilized for enrolling participants in clinical trials, we acknowledge that studying subjective cognitive complaints, low cognitive test scores, and neurobehavioral symptoms across serial evaluations is a needed next step for defining the early stages of the AC.[38] Lastly, we chose to focus on amyloid biomarkers due to their particular role in determining whether an individual is on the AC.[1] However, the NIA−AA framework also includes other biomarkers for neurodegeneration (e.g., volumetric MRI indices) and tau deposition (e.g., tau-PET and CSF phosphorylated tau measures) that require further study. In addition, it will be important to examine the influence of comorbidities, such as cerebrovascular pathology, on classification rates.[39]

Conclusions

This study provided an initial empirical operationalization of the early stages of the AC based on the symptoms proposed in the new NIA−AA research framework. Rates of subjective cognitive complaints and neurobehavioral symptoms appeared similar across A+ and A− groups, whereas low cognitive test scores were clearly more common in the A+

group. About half of the sample of A+ individuals demonstrated at least 1 symptom class, whereas ~7% exhibited all 3 types of symptoms. Consequently, AC stage 2 may be best defined by a moderate standard, wherein 2 symptom domains are required for diagnosis (with AC stage 1 defined as meeting fewer than 2 criteria), as this standard could provide the best balance between false negatives and false positives. More research on classification accuracy and rates of conversion is needed to provide empirical support for this assertion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic Statistics of the Sample by Amyloid Status

	Total Sample	A+	A−
n	548	101	447
Age: *M* (*SD*)	71.68 (8.06)	73.80 (6.94)	71.21 (8.23)
Education: *M* (*SD*)	16.42 (2.63)	16.32 (2.45)	16.45 (2.67)
% Female	58.40%	55.40%	59.10%
% White	86.90%	94.10%	85.20%

Table 2

Subjective Cognitive Decline and Neurobehavioral Symptoms as Reported by Clinicians, Caregivers, and Patients by Amyloid Status

Subjective Cognitive Decline				
	A+	**A−**	χ^2	***p***
Clinician Reported	11.90%	9.20%	.69	.405
Caregiver Reported	14.40%	10.60%	1.13	.288
Self-Reported	28.70%	21.70%	2.29	.130
Any Reporter	39.40%	29.90%	3.33	.068
Neurobehavioral Symptoms				
Clinician Judgment				
	A+	**A−**	χ^2	***p***
Depression	6.90%	5.60%	.49	.783
Anxiety	5.90%	5.60%	.02	.891
Apathy	3.00%	2.50%	.09	.77
Caregiver Reporter (NPI-Q)				
	A+	**A−**	χ^2	***p***
Depression	3.10%	10.10%	4.91	.027
Anxiety	12.20%	10.10%	.40	.529
Apathy	3.10%	3.90%	.17	.682
Self-Reported				
	A+	**A−**	χ^2	***p***
Depression	4.00%	5.00%	.18	.674
Any Reporter				
	A+	**A−**	χ^2	***p***
Any Neurobehavioral Symptom	22.40%	22.40%	0.00	.990

Note. NPI-Q = Neuropsychiatric Inventory Questionnaire

Table 3

Mean Demographically-Adjusted z-Score on Cognitive Tests for A+ and Negative Groups Diagnosed as Cognitively Intact

Test	*t*	*P*	*M (SD)* A+	*M (SD)* A−	*d*
Craft Story Immediate Recall	.52	.605	−.09 (1.26)	−.02 (1.00)	.06
Benson Figure Copy	1.16	.248	−.34 (1.29)	−.18 (1.00)	.14
Number Span Forward	2.99	.003	−.43 (1.05)	−.01 (1.00)	.33
Number Span Backward	2.17	.030	−.17 (1.09)	.07 (1.00)	.24
Animal Fluency	1.46	.144	−.22 (.97)	−.06 (1.00)	.16
Vegetable Fluency	−.34	.734	.15 (1.06)	.11 (1.00)	−.03
Trailmaking Part A	2.46	.015	−.39 (1.53)	.01 (1.00)	.31
Trailmaking Part B	2.19	.031	−.61 (2.72)	−.00 (1.00)	.30
Craft Story Delayed Recall	.35	.729	−.10 (1.00)	−.05 (1.00)	.04
Benson Figure Recall	.11	.318	−.21 (1.12)	−.10 (1.00)	.11
Confrontation Naming	.40	.687	.08 (1.28)	.13 (1.00)	.04
Letter Fluency	−.25	.80	.05 (1.01)	.03 (1.00)	−.03

Note. Trailmaking Parts A and B recoded, such that a lower score indicates worse performance.

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Table 4

Base Rate of AC Stages by Different Diagnostic Standards among A+ Individuals Diagnosed as Cognitively Normal

Standard for AC Stage 2	Base Rate for Meeting Standard for AC Stage 2	Base Rate for Meeting Standard for AC Stage 1
At least 1 criterion met	57.40%	42.60%
At least 2 criteria met	28.70%	71.30%
All 3 criteria met	6.90%	93.10%

Note. In this framework, AC Stage 1 would be defined by not meeting the standard for AC Stage 2.

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