Received: 18 December 2023 | Accepted: 19 December 2023

DOI: 10.1002/dad2.12540

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

ADCOMS sensitivity versus baseline diagnosis and progression phenotypes

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

BACKGROUND: The Alzheimer's Disease COMposite Score (ADCOMS) is more sensitive in clinical trials than conventional measures when assessing pre-dementia. This study compares ADCOMS trajectories using clustered progression characteristics to better understand different patterns of decline.

METHODS: Post-baseline ADCOMS values were analyzed for sensitivity using mean-to-standard deviation ratio (MSDR), partitioned by baseline diagnosis, comparing with the original scales upon which ADCOMS is based. Because baseline diagnosis was not a particularly reliable predictor of progression, individuals were also grouped into similar ADCOMS progression trajectories using clustering methods and the MSDR compared for each progression group.

RESULTS: ADCOMS demonstrated increased sensitivity for clinically important progression groups. ADCOMS did not show statistically significant sensitivity or clinical relevance for the less-severe baseline diagnoses and marginal progression groups.

CONCLUSIONS: This analysis complements and extends previous work validating the sensitivity of ADCOMS. The large data set permitted evaluation–in a novel approach–by the clustered progression group.

KEYWORDS
ADCOMS, Alzheimer's Disease, clustering, longitudinal change

1 | BACKGROUND

The Alzheimer's Disease COMposite Score (ADCOMS) assessment scale was originally developed to better identify early dementia progression in the context of efficient and effective pharmacological trials planning, and to monitor progression in pre-symptomatic and prodromal cases likely to benefit from early trial interventions.[1] To this end, ADCOMS is one of several composite scores aimed at improving trial efficiency and establishing more effective trial endpoints,[2,3] particularly with growing interest in anti-amyloid interventions targeted at early to mild dementia cases.[4,5] Composite scales such as ADCOMS re-purpose responses from existing assessments, reducing some of the effort required to introduce and validate new approaches. Despite questions about the theoretical basis of composite scales, their data-driven approaches, and their mathematical derivations,[2,3,6] ADCOMS has been used with good results in several studies alongside conventional scales.[7,8]

ADCOMS is a weighted composite of responses from the 13-item version of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Mini-Mental State Examination (MMSE), and the Clinical Dementia

Rating Sum of Boxes (CDR-SB) assessment.[1] The composite was constructed analytically, identifying the most useful item responses using partial least squares (PLS) regression. In the original work,[1] ADCOMS sensitivity was compared with existing assessment instruments using mean-to-standard deviation ratio (MSDR), the ratio of the mean difference of change with the standard deviation (SD) of those differences. MSDR, therefore, describes change in terms of z-scores, and is a familiar metric in assessing clinical change over time in several neurological research areas.[9–11]

The original study describing the development of the ADCOMS was based on data from 1160 subjects, collated from four different studies, of which 405 were from Alzheimer's Disease Neuroimaging Initiative (ADNI; downloaded May 2010). These were augmented with data from placebo groups from three, unrelated, donepezil-based intervention trials. Primary results were reported at 12 months,[1] with a graphical supplement showing results over 36 months.

In contrast, the analysis reported here used solely ADNI data in deriving ADCOMS trajectories for 2263 individual subjects (downloaded December 2020), with a rich mixture of baseline diagnoses. This data set, therefore, provided a more-consistent basis for interpretation. The large sample size provided greater statistical power, allowing subgroup analysis. Sensitivity was assessed initially against baseline diagnosis category (validating and extending the previous work), and in a novel step reported here by clustered progression rate group.

We show that ADCOMS sensitivity makes it appropriate for use in dementia research, particularly for subjects with more-definitive diagnoses and faster progression trajectories. Increased assessment sensitivity potentially allows predictors of more-rapid progression to be identified, assisting in improved individual prognosis, which could in the future support tracking of medication efficacy.[12,13] We also show that in settings where ADCOMS may be difficult to administer, CDR-SB remains a practical approach with limitation characteristics better informed by this analysis.

RESEARCH IN CONTEXT

1. **Systematic review**: Longitudinal trajectories of decline in dementia generally use conventional assessment scales. These often have limited sensitivity, affecting prognosis, risk group identification in predictive modeling, and monitoring intervention benefits.
2. **Interpretation**: Alzheimer's Disease COMposite Score (ADCOMS) trajectories demonstrate considerable sensitivity to change when analyzed by progression rate group, derived using longitudinal clustering algorithms, complementing previous results by baseline diagnosis.
3. **Future directions**: Clinical research will benefit from using more-sensitive outcome measures to identify risk factor groups during pre-clinical stages of dementia, particularly with novel interventions.

2 | METHODS

This section introduces the data set's main characteristics. The method for calculating ADCOMS is summarized, along with a description of the method for clustering individual ADCOMS trajectories into progression rate groups. Use of MSDR to compare scale sensitivity is described for baseline diagnosis categories and for the derived progression rate groups.

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

2.1 | Baseline data summary

The data were obtained from the ADNI database for assessments up to November 2020 for 2256 subjects in the ADNI trial. Trial subjects were typically 73.5 years old (min 54.4; max 91.4) with more male (1214 vs 1071) than female subjects. The average age of female participants was 72.6 years compared to 74.1 years for male participants. Those with a subjective memory complaint (SMC) or early mild cognitive impairment (EMCI) baseline diagnosis were slightly younger (71.6 and 71.0 years), whereas the cognitively normal (CN) and AD baseline diagnoses cohorts were slightly older (74.5 and 75 years, respectively). The proportions of female and male participants vary for each baseline diagnosis category, from 38.3% to 61.7%, and conversely.

This constitutes a varied mix of baseline diagnoses in these data, including a considerable contingent of CN and SMC subjects (Table 1). Although ADNI trial recruitment was not intended to replicate proportions typical of clinical or community settings, the ADNI trial data and, therefore, the analysis here includes a wide variation of subject types.

2.2 | Subject follow-up assessments

Data were analyzed from baseline up to month 36, giving a maximum of six assessments per subject. Follow-up coverage varied by baseline diagnosis. Only the late MCI (LMCI) cases had assessments at 18 months; otherwise there was good coverage up to 24 months, with up to 36 months for CN and MCI categories (Table S1).

In general, there were relatively few changes in follow-up diagnosis over time. Of the 812 CN and SMC baseline subjects, for example, there were only 56 MCI and 6 dementia diagnoses that were updated at follow-up (Table S2). In comparison, of the 651 subjects with an LMCI baseline diagnosis, 241 were diagnosed with dementia at some point. This lack of granularity using baseline

TABLE 1 ADCOMS value ranges at baseline (per Figure 2) and over 36 months.

	Baseline			Over 36 months		
Baseline diagnosis	Median	Max	Subjects	Median	Max	Data points
CN	0.040	0.173	514	0.040	0.730	1291
SMC	0.045	0.199	295	0.044	0.511	623
LMCI	0.140	0.576	391	0.136	0.946	1458
EMCI	0.210	0.615	651	0.263	1.770	2858
AD	0.570	1.196	381	0.646	1.675	1126

Abbreviations: AD, Alzheimer's Disease; CN, cognitively normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; SMC, subjective memory complaint.

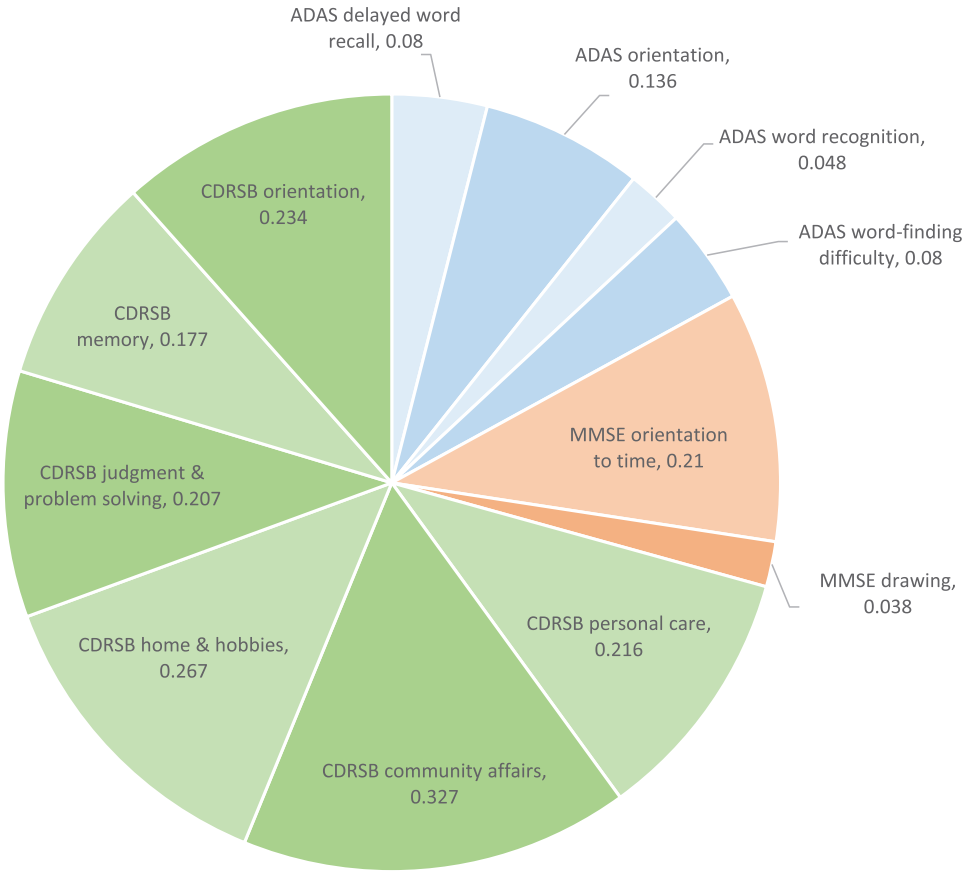

FIGURE 1 ADCOMS components showing maximum contributions to the overall score.

diagnosis was, therefore, a key motivation for the longitudinal approach used in this study, revealing more about the dynamics of dementia progression.

2.3 | ADCOMS score components

ADCOMS scores for each subject at each assessment time point were calculated from the constituent item scores extracted from several ADNI files (listed in the supplement preamble). The method for calculating ADCOMS is described comprehensively elsewhere[1,14]; however, Figure 1 shows ADCOMS' maximum contributions from each of the item responses, weighted by the relevant coefficient. All items have a cognitive or functional focus. All six items from CDR-SB contribute 70% of the overall ADCOMS, ADAS-Cog contributes 1/6, and MMSE contributes 1/8. The scores from the two MMSE items are reversed from conventional use for consistency with ADAS-Cog and CDR-SB.

The weighted sum of CN item scores will be less than for those with MCI, and only the most severe dementia cases will have the highest ADCOMS score. In its final form, the ADCOMS scale extends from 0 up to 1.97 as cognitive and functional severity increases.

(Table S3 compares the derived baseline ADCOMS values with the original scales.)

The ADCOMS values over time were combined with several demographic variables for each subject. The prepared data included subject identifier, sex, baseline age, baseline diagnosis, visit index, and follow-up diagnosis, as well as scores on the original ADAS-Cog, MMSE, and CDR-SB scales. Data were stored in long format, whereby individual trajectories were in consecutive rows.

2.4 | Clustering individual ADCOMS trajectories into progression rate groups

From this data set, progression groups having similar longitudinal trajectories over 36 months were identified. The trajectory for each subject was partitioned into one of a number of groups sharing similar progression characteristics using a clustering algorithm developed for real-world (i.e., noisy and incomplete) longitudinal data. The *curveRep()* algorithm in the *Hmisc* package[15] in Rstudio[16] was used. This algorithm is based on well-known clustering methods,[17] using medoids for robustness and generalizability. The *curveRep()* algorithm handles time responses with missing data and varying sample sizes per trajectory.

The number of resulting clusters was set to four, a value informed by previously published work on progression rate groups.[18] Setting this parameter a priori is established practice in clustering analysis. The clustering algorithm distance method was "Euclidean" with default *curveRep()* settings.

2.5 | Progression group characterization

To characterize the progression groups resulting from the clustering process, the data points in each group were fitted to a simple linear regression model. This was done using the formula *ADCOMS* ~ *assessment month* with the Ordinary Least Squares *lm()* function in R to give intercept and slope values (β_0 and β_1). Although progression was not necessarily expected to be linear, this simple approach captured the essential characteristics.

The resulting groups were labeled "fast," intermediate ("intm"), and "slow." These label names were a convenient indication of the dominant group characteristic: that is, progression rate (the linear slope of the trajectory) in terms of ADCOMS units per unit time. A stable, non-progressing group ($n = 733$, 38.7%) was allocated the "none" label. Single point "trajectories" ($n = 360$) were excluded from the clustering analysis.

2.6 | Sensitivity analysis by baseline diagnosis and progression group using MSDR

The method used to analyze ADCOMS sensitivity was consistent with the original paper, using the mean-to-standard deviation (or MSDR) of change. The reference datum was baseline, and for each follow-up assessment the MSDR was calculated and compared to the MSDR on the original ADAS-Cog, MMSE, and CDR-SB scales as a ratio of MSDR values (so, strictly speaking, a ratio of ratios).

Statistical significance was confirmed on the ADCOMS and original scales using the paired two-sample *t*-test (i.e., before-and-after paired-difference test). For clarity, comparisons are reported here only where paired *t*-tests were both significant at the 0.10 level. This is a reporting inclusion criterion for tabulation rather than an inference threshold. Full results are given in the supplement (Section S.5), along with a brief discussion on combined/aggregated *p*-values (Section S.6).

To allow comparison with the original ADCOMS work, results are presented first by baseline diagnosis. Further results are then presented using the same MSDR analysis method applied to the progression groups.

3 | RESULTS

To provide a sense of ADCOMS trajectory value ranges, this section first summarizes ADCOMS values by diagnosis category. An assessment of sensitivity is then presented over follow-up, partitioned by baseline diagnosis. The progression characteristics of the groups resulting from the clustering analysis are then summarized, followed by the progression group sensitivity assessment.

3.1 | ADCOMS values by baseline and follow-up diagnosis

ADCOMS value ranges at baseline are illustrated in the boxplot in Figure 2, taking all 2232 baseline data points. This shows the relationship between the five baseline diagnosis categories (used only at recruitment) and the three follow-up diagnosis categories in ADNI. Values are plotted on a log scale to show value ranges and extent of overlap. For example, subjects with a CN or SMC baseline diagnosis ($n = 514$ and $n = 295$) fall into the CN follow-up diagnosis category, with similar median baseline ADCOMS values (0.040 and 0.045). Median MCI values are higher than CN (0.14 and 0.21 for EMCI and LMCI, respectively), and higher still for median AD (0.57) at baseline. Baseline assessment values on ADCOMS, ADAS-Cog, MMSE, and CDR-SB scales are reported in Table S3.

Over 36 months of follow-up, ADCOMS maximum values (Table 1) increase considerably, particularly for the less-severe baseline diagnoses. Changes in median values are in general fairly modest. This smearing of value ranges—resulting from mixed progression types within the baseline diagnosis categories—suggests that baseline diagnosis is not a particularly informative categorization. This insight prompted the use of a clustering method reported in Section 2.5 as an alternative trajectory-grouping approach.

3.2 | Sensitivity analysis over time by baseline diagnosis

Comparing progression on the ADCOMS scale with the three original scales provides the results shown in Table 2. Results are partitioned

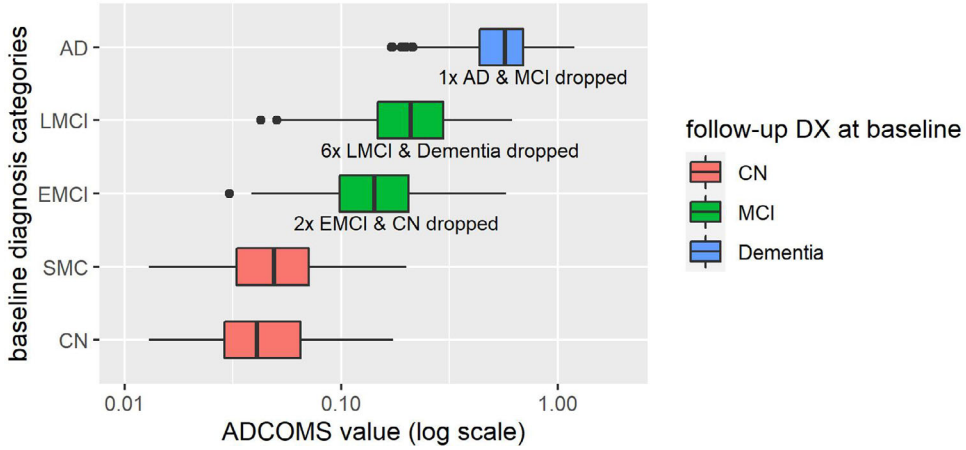

FIGURE 2 ADCOMS value ranges by baseline diagnosis category, with color fill by follow-up diagnosis category at baseline. There were several inconsistent combinations, where the three follow-up diagnosis categories were not consistent with the five baseline diagnosis categories. These are indicated in the figure and were excluded (i.e., dropped) from the calculations.

over time for the five different baseline diagnosis types and are shown where the ADCOMS scale and the original scale both exhibit statistically significant changes from baseline. Blank cells indicate non-significant changes either in the original assessment scale or in ADCOMS, or both. The supplement provides full results, including statistically non-significant changes (Table S10A and Figure S4).

For EMCI, LMCI, and AD baseline diagnoses, ADCOMS is considerably more sensitive than the original scales, especially for ADAS-Cog and MMSE. Versus ADAS-Cog, the sensitivity comparison with ADCOMS reduces over time, particularly for LMCI. For EMCI, the comparison with ADCOMS increases at later visits. Lower MSDR values versus CDR-SB is perhaps not unexpected, as ADCOMS is strongly associated although weighted.

For CN and SMC subjects, the ADCOMS scale is statistically less sensitive than CDRSB. This is likely due to the "noisy" contribution of the relevant ADAS-Cog and MMSE item scores. The anomalous negative MSDR value versus ADAS-Cog at month 12 for CN cases is due to a statistically significant negative change on the ADAS-Cog scale. Clinical relevance in these CN and SMC cases is likely to be limited, however, as suggested by the small changes in successive mean values (Table 2; column 3) with reference to the 0.05 cutoff value over 12 months proposed by Tahami Monfarad et al.[19]

Based on a much larger and consistent sample, although with different partitioning, these tabulated results compare well with the plotted results in Wang et al.[11]

3.3 | Progression rate group characteristics after longitudinal clustering

Post-clustering analysis shows that although baseline diagnosis was associated with progression groupings, there was limited correspondence. There was considerable overlap between categories (Table S4 and Figure S1), particularly for MCI diagnosis categories. Clustering the trajectories into similar groups, therefore, allowed an alternative and more-insightful analysis.

Scatterplots of each progression group are shown in Figure 3. Data points show the ADCOMS score at each visit for 1895 subjects. These are jittered to avoid over-plotting, as the real data align with the time point. The bold lines show the mean ADCOMS values, determined by a simple linear regression formula. The coefficients and sample sizes for the regression fits are reported in the supplement (Tables S7 and S8).

3.4 | Sensitivity analysis over time by progression rate

Table 3 summarizes ADCOMS sensitivity compared to the original scales, by assessment month and partitioned by progression group. Color shading again indicates the magnitude of the comparison, where darker green indicates greater sensitivity, gray somewhat improved sensitivity, and red indicates lower sensitivity versus the original scale. Full results are provided in the supplement (Table S10B and Figure S4).

ADCOMS is clearly much more sensitive to progression than ADAS-Cog and MMSE for fast and intermediate progression types, and this is consistent over 36 months, with similar numerical results for ADAS-Cog and MMSE. ADCOMS is also more sensitive than CDR-SB for fast and intermediate types, although the comparison is somewhat closer. This is again likely due to the greater dependence on CDR-SB item scores in the ADCOMS calculation. For slow types, significance criteria are met only after 24 months. ADCOMS is less sensitive for many non-progressors, but as the mean ADCOMS values show (Table 3; column 3), clinical relevance is likely to be limited.[19]

In comparison with baseline diagnosis categories, clustered progression trajectory groups have a more consistent and symmetrical structure, lower heteroscedasticity, shorter boxplot tails, and fewer outliers than baseline diagnosis categories (Figure S3).

TABLE 2 Baseline diagnosis MSDR sensitivity ratios comparing ADCOMS to the three original scales, by visit month.

Baseline diagnosis	Visit month	Mean ADCOMS	Ratio of MSDR values		
			ADAS-Cog	MMSE	CDR-SB
CN	m00	0.046			
	m06	0.050			0.63
	m12	0.051	−0.91		0.63
	m24	0.056			0.78
	m36	0.066			0.76
SMC	m00	0.053			
	m06	0.062			1.10
	m12	0.071			
	m24	0.061			0.63
	m36	0.148		1.06	
EMCI	m00	0.160			
	m06	0.161		0.71	
	m12	0.163		0.86	
	m24	0.174		1.55	1.20
	m36	0.186	2.39	1.71	1.33
LMCI	m00	0.228			
	m06	0.271	2.28	1.33	1.14
	m12	0.301	2.26	1.73	1.12
	m18	0.355	1.57	1.73	1.16
	m24	0.383	1.34	1.35	1.09
	m36	0.434	1.28	1.24	1.09
AD	m00	0.573			
	m06	0.661	1.19	1.73	1.10
	m12	0.747	1.16	1.45	1.13
	m24	0.898	1.07	1.43	1.06
	m36	1.154	1.32	2.12	0.96

Clinical relevance can be determined by ADCOMS mean value. Populated cells are for statistically significant differences. Green shading indicates where the ADCOMS shows more sensitivity; red shading shows less sensitivity. ADCOMS is consistently more sensitive than the other scales for EMCI at 24 months and beyond, and for LMCI and AD at all time points, noting that SMC and AD baseline categories at 36 months consist of only nine assessments.

Abbreviations: AD, Alzheimer's Disease; CN, cognitively normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; SMC, subjective memory complaint.

TABLE 3 Progression group MSDR sensitivity comparisons, otherwise as Table 2 regarding clinical relevance, cell value inclusion, and color fills.

Progression group	Visit month	Mean ADCOMS	Ratio of MSDR values		
			ADAS-Cog	MMSE	CDRSB
None	m00	0.053			
	m06	0.051			
	m12	0.050	0.55		1.10
	m18	0.069	1.13		0.74
	m24	0.048	0.68		
	m36	0.053	0.65		0.86
Slow	m00	0.154			
	m06	0.153			
	m12	0.150			
	m18	0.173			
	m24	0.164	1.48		
	m36	0.175			1.27
Intermediate	m00	0.277			
	m06	0.325	1.68	1.54	1.20
	m12	0.355	1.87	2.16	1.11
	m18	0.370	1.48	2.25	1.24
	m24	0.427	1.37	1.76	1.08
	m36	0.479	1.65	1.53	1.12
Fast	m00	0.539			
	m06	0.656	1.47	1.34	1.14
	m12	0.754	1.46	1.42	1.19
	m18	0.708	1.98	1.69	1.18
	m24	0.922	1.56	1.53	1.09
	m36	0.993	1.63	1.59	1.14

ADCOMS is more sensitive for the Slow group in very limited circumstances, and at all time points for Intermediate and Fast progression groups.

4 | DISCUSSION

Trajectories of decline, embodied in progression rate models, are used in several neurological conditions,[20–22] aimed at improving patient care, health care service delivery, clinical practice, biomarker identification, risk factor research, and trials designs.[12] This is also the case for longitudinal models of AD,[23–25] contrasting and complementing more conventional staging models,[26] which somewhat misrepresent dementia severity as a sequence of discrete states.

Comprehensive understanding of progression trajectory, particularly in the early and more subtle stages of disease progression, has been shown to better identify subjects for clinical trials and in monitoring of drug-intervention effects, where novel anti-amyloid therapies[27] are administered in preclinical and prodromal cases. The underlying considerations will likely apply eventually to similar interventions in clinical practice.

We show that ADCOMS provides a sensitive measure of early neurological change, particularly for groups exhibiting common progression characteristics. Small progression changes require more-sensitive assessment methods to identify continued or paused decline, allowing for more-nuanced assessment of prognosis and monitoring.

There are challenges, however, with ADCOMS as currently implemented. These concern a proper psychometric basis[2,3] as well as its administration time. Interview context, question item ordering, and duplicated domains (e.g., orientation and constructional praxis) may be

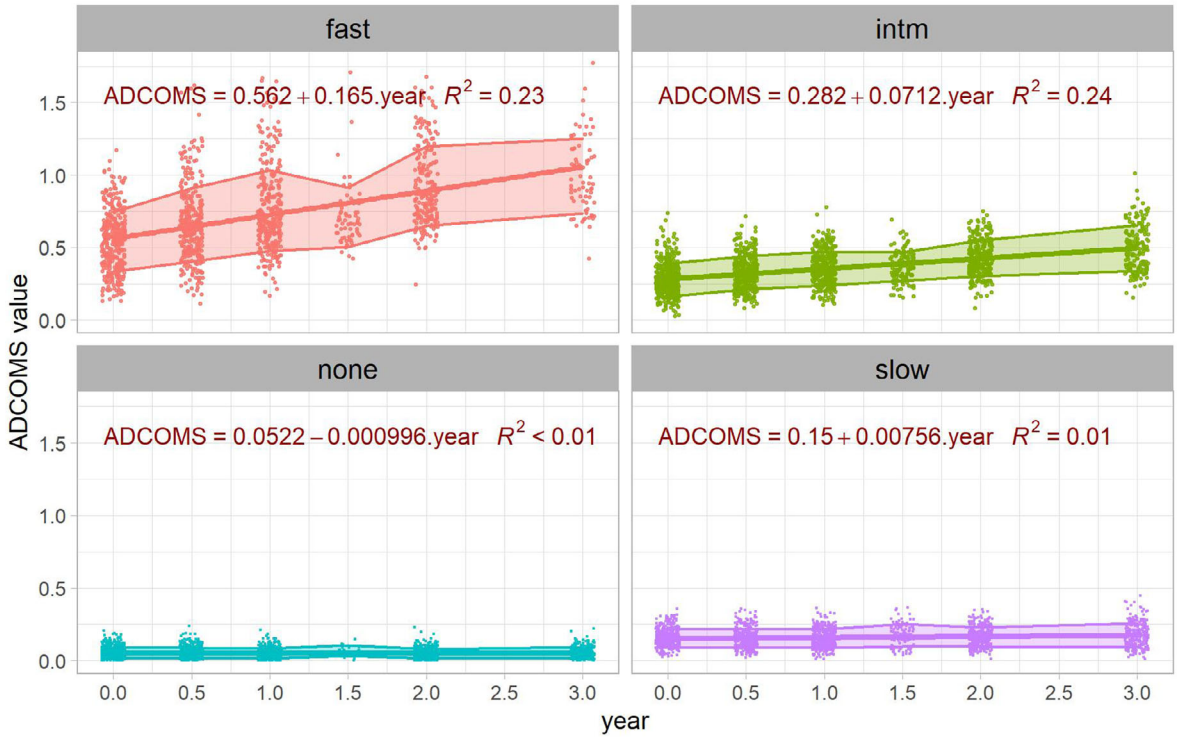

FIGURE 3 Scatter plots of data points clustered using individual trajectories, with ribbons showing mean value and SD progression over time (1895 subjects, 7625 data points). Panes are ordered clockwise.

important latent factors. Because some sources suggest that ADAS-Cog and CDR-SB may take up to 45 and 90 min, respectively,[28–30] this makes use difficult to justify outside of research.[31] Rater certification requirements add further complexity. A time-optimized version of ADCOMS—removing duplicated and unused items—is nevertheless an intriguing prospect. Such an approach would require validation, particularly to understand the effect of questions conducted over a shorter duration, and possibly lower informant stress (or distress).

Our results show how well CDR-SB sensitivity compares with ADCOMS, and it, therefore, remains expedient both for stand-alone assessment as well as a precursor in potential anticipation of the full ADCOMS. We also show the substantial sensitivity shortfall compared with MMSE, which is much faster to administer and commonly used in various contexts, including clinical practice. This would make MMSE less appropriate where assessment sensitivity is an important goal.

In terms of trajectory clustering results, progression group characteristics provide useful additional insights, complementing stratification by baseline diagnosis. Although EMCI, LMCI, and AD categories can be readily distinguished from CN and SMC, similarly fast and intermediate progression groups can be compared to slow- and no-progression groups. Such knowledge may better inform individual prognosis and response to interventions.

Better insights into progression dynamics, as provided by these results, therefore, have potentially considerable implications for clinical trials, where tracking faster or slower progression types complements follow-up using conventional outcome measures and endpoints.[1] The benefit of properly targeted disease-modifying therapies on specific target groups within trials is a considerable advantage, improving trial efficiency and efficacy, increasing effect size and statistical power, while mitigating costs and duration. There is also potential for use with pre-symptomatic treatments, where it may be possible to track CN and SMC baseline types to an EMCI or LMCI trial endpoint,[32] or track patients within a progression rate group, complementing prognosis using staging scales.

The limitations of this study include the use of a data set from a single source. Although providing greater statistical power than originally reported,[1] there may be a loss of generalizability despite the wide-ranging recruitment policies in ADNI. To characterize the progression groups, simple regression approaches were used for ease of interpretation. Skewness assessment of pre- and post-transformed ADCOMS values did not provide better overall insights (or reveal any major issues). Work is underway to improve the regression fits, with additional predictors and the inclusion of random effects. However, simple models allow easy interpretation. Although the choice of four progression groups was based on previous research in several studies, more clusters may better reveal underlying characteristics and hence predictors of the more finely partitioned progression groups.

AUTHOR CONTRIBUTIONS

The lead author is a visiting research fellow working with the co-authors and their research team, in support of a program of

projects at the University of Southampton and University Hospital Southampton.

ACKNOWLEDGMENTS

Sofia Michopoulou is funded through an Integrated Clinical Academic Lectureship by Health Education England/National Institute for Health and Care Research (NIHR301287). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.;Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.;Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

How to cite this article: Evenden D, Prosser A, Michopoulou S, Kipps C. ADCOMS sensitivity versus baseline diagnosis and progression phenotypes. *Alzheimer's Dement*. 2024;16:e12540. https://doi.org/10.1002/dad2.12540