The Journal of Prevention of Alzheimer's Disease 12 (2025) 100261

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

The Alzheimer's Disease Cooperative Study – Activities of Daily Living dependence score: revision and validation of an algorithm evaluating patient dependence across the spectrum of AD severity

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ARTICLE INFO

Keywords:
Alzheimer's disease
Dependence
Alzheimer's Disease Cooperative
Study-Activities of Daily Living scale
Care partner

ABSTRACT

Background: Increasing dependence on informal and formal caregivers in Alzheimer's disease (AD) contributes to high societal cost. Treatments that delay time to increased dependence/care needs would be clinically meaningful, but these outcomes are rarely collected in early AD clinical trials. The 2015 ADCS-ADL dependence algorithm was created to estimate level of dependence in AD.
Objectives: To revise the original dependence algorithm to improve accuracy of dependence scores (DS) across AD severity, including early symptomatic AD.
Design: Secondary data analysis
Setting: Community cohort; randomized clinical trial
Participants: 14,000 participants enrolled across GERAS-EU observational study and 12 AD clinical trials.
Measurements: Three-phase algorithm revision: 1) reassess ADCS-ADL items to identify those appropriate for assessing dependence; 2) (a) assign individual item responses to degrees of assistance and (b) to operationalize assignment of DS based on extent of total assistance needed; and 3) validate revised algorithm in multiple datasets across AD severity from mild cognitive impairment due to AD to moderate-severe AD.
Results: The revised DS (0-6) algorithm classified most participants with early symptomatic AD as independent or moderately independent (DS<3) at baseline. With disease progression over time, the proportion of participants who were mildly to fully dependent (DS≥3) increased across AD severity. Increased DS was associated with incremental worsening of clinical outcomes.
Conclusions: The revised ADCS-ADL DS algorithm provides a supplementary approach to evaluate the impact of emerging treatments on independence/care needs in AD and may be useful in clinical trials where the ADCS-ADL has been collected.
Clinical trial registration information: EXPEDITION 1 NCT00905372; EXPEDITION 2 NCT00904683; EXPEDITION 3 NCT01900665; AMARANTH NCT02245737; TRAILBLAZER-ALZ NCT03367403; TRAILBLAZER-ALZ 2 NCT04437511; GRADUATE I NCT03444870; GRADUATE II NCT03443973; CREAD NCT02670083; CREAD 2, NCT03114657; TAURIEL NCT03289143; LAURIET NCT03828747

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https://doi.org/10.1016/j.tjpad.2025.100261
Received 27 February 2025; Received in revised form 1 June 2025; Accepted 22 June 2025
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1. Introduction

Dependence in Alzheimer's disease (AD) is a unifying representation of disease progression capturing the measurable, real-world impact of disease-related changes in cognition, function, and behavior on an individual's need for assistance in activities of daily living [1,2]. As AD progresses, the need for home assistance or institutional care increases, leading to higher rates of healthcare utilization, increased total care costs, and reduced quality of life [3–7]. Assessment and monitoring of patient dependence, including the nature and extent of supportive care needs, can provide clinically meaningful insights into the societal impact of AD progression. To date, few studies have explored the gradual loss of independence and associated increase in care needs/dependence on others in the early symptomatic stages of AD.

In 1994, Stern et al. published the Dependence Scale for use in AD [8]. Despite the importance of this concept in AD, the Dependence Scale has not been broadly used in AD clinical trials. In an effort to describe emergent dependence among clinical trial participants with AD, Kahle Wrobleski et al developed an algorithm [9] to classify participants into distinct levels of dependence based on item-level responses from the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) [10], a care partner-reported measure of daily functioning that is widely used in AD clinical trials. The ADCS-ADL scale includes 23 items assessing basic and instrumental activities of daily living (**Table S1**). Using data from the GERAS-EU observational study among individuals primarily with mild to moderately severe/severe AD, Kahle Wrobleski et al mapped the ADCS-ADL item responses onto 6 levels of dependence (**Table S1**) [9]. Among individuals primarily with mild to moderately severe/severe AD, a significant relationship was reported between assigned level of dependence derived from the ADCS-ADL score and the Mini-Mental State Examination (MMSE) (i.e., lower MMSE scores were associated with higher levels of dependence). The authors suggested that the ADCS-ADL-derived dependence levels could be used as appropriate interim clinical milestones to translate a functional scale to a level of dependence. A follow-up longitudinal analysis demonstrated that changes in these dependence levels over 18 months were associated with clinical progression, especially among individuals with more advanced cognitive impairment at baseline, those living with others, and those with multiple caregivers [11]. Furthermore, total societal costs of care also increased with greater dependence during the 18-month observation period [11].

The need for revision of the 2015 ADCS-ADL dependence mapping algorithm was identified through independent, concurrent observations by members of the authorship team who noted the frequent inaccuracy and/or clinical implausibility of dependence levels derived using the 2015 algorithm [9] in individuals with early symptomatic AD, inclusive of mild cognitive impairment (MCI due to AD) and mild AD. Specifically, dependence level classifications were consistently higher than expected, often failing to align with both clinical staging and observed performance on standard measures of cognition and function.

An in-depth analysis of ADCS-ADL items contributing to dependence levels >2 in MCI due to AD or mild AD participants revealed shortcomings within the 2015 algorithm underlying misassignment of largely independent individuals to inaccurate (higher than expected) dependence levels (**Figure S1**). First, individuals with minimal or no impairment in instrumental ADL (iADL) were erroneously classified as dependence level 3 (connoting significant loss of autonomy) if they failed to perform at ceiling (i.e., achieve the best possible score) on *all items* assessing basic ADLs (bADLs). However, because below-ceiling scores on bADL items can reflect very minor changes (e.g., reduced speed/efficiency) or physical disabilities independent of cognition, participants who remained fully independent in iADL were vulnerable to misclassification. ADCS-ADL items contributing to dependence level >2 in MCI due to AD and mild AD participants are shown in **Tables S2 and S3**. Second, the 2015 algorithm failed to account for variations in the number and content of response options on individual ADCS-ADL items, classifying item scores of <2 as impaired, despite the fact that some items are binary (score range 0-1), while others have broader range of item scores (e.g., 0-4). A final shortcoming of the 2015 algorithm was incorporation of all items from the ADCS-ADL, including several items not directly related to dependence (ability to recall a TV program, ability to pay attention to small talk/engage in conversation, ability to talk about current events, and ability to read magazine/book >5 min).

The current paper describes the revision of the 2015 ADCS-ADL dependence mapping algorithm to improve accuracy in estimating patient dependence across the AD spectrum of severity, including individuals with early asymptomatic AD. The three-phase algorithm revision included 1) review of each ADCS-ADL item to determine its relevance to the concept of dependence, 2) refinement of the original Kahle-Wrobleski et al. [9] theory-driven dependence levels and assignment of individual item responses to levels of assistance required for the algorithm, and 3) validation of the revised algorithm using the original GERAS-EU dataset [9,11] and recent clinical trial datasets in biomarker-confirmed individuals with MCI due to AD, mild, or moderate AD.

2. Methods

2.1. Algorithm revision

Development of the revised ADCS-ADL Dependence Score algorithm was completed in 3 phases that were conceptually driven and consensus led. During Phase 1, each item within the ADCS-ADL scale (**Table S1** ADL questions) was reviewed to assess relevance to the concept of dependence. Decisions regarding inclusion/exclusion of items within the revised algorithm were made by consensus. Potential incorporation of ADL functional "domains," reflecting specific groupings of items derived from factor analysis of the ADCS-ADL scale and utilized in the 2015 algorithm was discussed; incorporation into the revised algorithm was ultimately rejected by consensus decision. These subdomains, originally identified through data-driven factor analyses of all items in mild to moderate AD, do not have clear application to earlier stages of clinical impairment or to item-based assessment of dependence and are not incorporated into standard use and interpretation of ADCS-ADL scores.

Phase 2 included (a) assignment of individual bADL and iADL item responses to levels of assistance required and (b) determination of dependence score based on both the number of iADLs and bADLs requiring assistance and the extent of assistance required (e.g., reminders, support, or physical help). Individual bADL and iADL item responses were mapped to the level of care needed as shown in **Table S4**. Dependence scores were then assigned based on the number of iADLs and bADLs within each level of care. Finally, the algorithm itself was specified to calculate the dependence score based on input of raw scores from the ADCS-ADL measure.

Phase 3 included execution of a three-step validation analysis plan (see datasets and statistical analysis sections), using historical data representing participants with AD across the spectrum of disease severity from MCI due to AD to moderate-severe AD.

2.2. Data sources

Secondary data analysis was performed using data from 14,000 participants collected across 13 completed studies, including 1 observational and 12 phase 2/3 randomized clinical trials (**Table S5**) [12–21]. Participants included those with biomarker-confirmed AD pathology and/or a clinical diagnosis of probable AD and represented a broad range of disease severity. Active treatments across the studies included solanezumab, lanabecestat, donanemab, gantenerumab, crenezumab, and semorinemab. Detailed descriptions of each study are available in the original publications [12–21].

2.3. Clinical outcome assessments

Validation of the revised algorithm examined the relationship between ADCS-ADL dependence scores and the following clinical outcomes assessed at baseline and end of study (Month 12 or 18). Specific key outcomes included in each study are provided in **Table S5**.

Mini-mental state examination (MMSE): brief rater-administered assessment of global cognitive status [22]. MMSE total scores range from 0 to 30, with lower scores indicating greater cognitive impairment.

Integrated Alzheimer's Disease Rating Scale (iADRS): The iADRS integrates 31 items from the ADAS-Cog_{13} (13 items) and the ADCS-iADL (18 items) to provide a single summary total score of global disease severity. The iADRS total scores range from 0 to 144 with lower scores indicating greater impairment [23,24].

Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog13): assesses severity of cognitive impairment in AD. The *ADAS-Cog13* total score ranges from 0 to 85, with higher scores indicating *greater* impairment [25].

Clinical Dementia Rating Scale (CDR): interview-based assessment of cognition and function. The CDR global score (CDR-GS) provides clinical staging of dementia from 0 (no impairment) to 3 (severe impairment). The CDR "sum of boxes" (CDR-SB) score sums clinical ratings across 6 domains, providing a continuous outcome with total scores that range 0 to 18, with higher scores indicating greater impairment [26,27].

Alzheimer's Disease Cooperative Study- Activities of Daily Living (ADCS-ADL): a 23-item informant-reported measure assessing patient performance on instrumental and basic activities of living over the past 4 weeks (**Table S1**). ADCS-ADL total scores range from 0-78, with lower scores indicating greater impairment in daily functioning [28].

Zarit Burden Interview (ZBI): a 22-item informant-reported measure assesses caregiver burden, including the impact of caregiving on psychological, social, and financial well-being. Total scores range from 0-88, with higher scores indicating greater care partner burden [29,30].

Neuropsychiatric Inventory (NPI-12, NPI-Q): informant-reported measure assessing neuropsychiatric symptoms (e.g., delusions, hallucinations, agitation, depression, anxiety, and apathy) via care partner reporting. Use of NPI-12 or NPI-Q varies by study (**Table S5**). NPI-12 total score ranges from 0-144, with higher scores indicating greater frequency/severity of symptoms) [31]. The NPI-Q provides total scores for symptom severity (0-36) and caregiver distress (0-60), with higher scores indicating greater severity/distress.

EQ-5D: assesses quality of life with total score ranging from 0-100, with lower scores indicating lower quality of life [32,33].

Resource Utilization in Dementia-Lite (RUD-Lite): derives care partner time in hours/month and total societal cost (monthly) [34].

2.4. Statistical analysis

Descriptive analyses were conducted to examine the distribution of ADCS-ADL dependence scores at baseline and each follow-up visit by baseline AD severity using frequencies and percentages. ADCS-ADL Dependence score shifts from baseline to Month 18 were also described based on baseline dependence scores and AD severity. To assess the relationship between ADCS-ADL Dependence Score and key clinical outcome measures, baseline mean scores with 95% confidence interval (CI) were reported for all the outcomes across each dependence score classification. Additionally, to quantify the relationship between the revised ADCS-ADL dependence score and key clinical outcomes, a similar approach to that used by Kahle-Wrobleski et al. [11] was applied to the GERAS-EU dataset. Pearson correlation analyses were conducted between the revised dependence score and outcomes at both baseline and Month 18. To examine the relationship between changes in dependence scores and changes in key clinical outcomes from baseline to Month 18, linear regression models were applied. These models were adjusted for baseline outcome measures, baseline ADCS-ADL total score, participant baseline characteristics (including AD dementia severity, country, age, gender, and number of comorbidities), and care partner baseline characteristics (age, relationship to participant [spouse: yes/no], and employment status [works for pay: yes/no]). To examine the relationship between care partner time and dependence score, Spearman's rank correlations between care partner time and dependence score were calculated overall, by disease severity level at baseline and through the last study visit, and by change from baseline to the end of study (for studies wherein care partner time was available).

For each study, AD severity level at baseline was defined using the MMSE and/or CDR-GS: MCI due to AD, mild AD, moderate AD, and moderate-severe AD. However, definitions of AD severity differed by analysis and study. For the first validation step, replication of the GERAS-EU analysis was completed using the originally described definitions of AD severity and included all participants with mild AD, moderate AD, and severe AD (**Table S5**) [9,11]. For the second and third validation steps, definitions of AD severity were revised to match those in the 12 clinical trials (**Table S5**) and only mild AD and moderate AD were included in GERAS-EU analysis.

SAS and R codes for the revised ADCS-ADL Dependence Score algorithm are provided in **Table S6**. Analyses were performed using Statistical Analysis Software Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) or R Statistical Software Version 4.2.2; R Core Team 2022.

3. Results

3.1. Specification of the revised algorithm

The following 4 ADCS-ADL items were excluded from the revised algorithm based on a consensus decision that they lacked direct relevance to the concept of dependence: Q8 (Watching TV), Q9 (pay attention to small talk/engage in conversation), Q19 (talk about current events), and Q20 (ability to read magazine/book >5 min).

Missing data rules were revised to improve accuracy of dependence score assignment. Specifically, the dependence score was set to missing if more than 2 iADL items or 1 bADL item was missing.

3.2. Phase 2

To facilitate assignment of dependence scores based on ADCS-ADL items with heterogeneous score ranges and response options, a framework was developed to consistently characterize the degree of care support associated with each item response option for the remaining 19 items (bADL and iADL) included in the revised algorithm (**Table S7**). Next, dependence scores were assigned based on the number of iADLs and bADLs requiring assistance and the extent of the assistance required (**Table S4**). The final revised algorithm (**Table S8**) provides direct mapping of ADCS-ADL responses to dependence score.

A key change in the revised algorithm was modification of the range of dependence scores from 6 (0-5 score) to 7 (0-6 score) in order to provide additional sensitivity to change across AD severity levels (Table 1).

3.3. Validation of the revised algorithm

3.3.1. GERAS-EU

Similar to the original algorithm [9,11], evaluation of the baseline distributions across AD severity using the revised algorithm shows that individuals with mild AD at baseline predominately had dependence scores of 2-4 compared to moderate-severe AD with dependence scores of 4-6 (**Figure S2**), with expected shifts at Month 18 across AD severity (Fig. 1). Overall, 61% of individuals with a dependence score of 3 at baseline transitioned to scores of 4-6 (with the majority transitioning to 4); and 47% of individuals with a dependence score of 4 at baseline transitioned to scores of 5-6 at Month 18, demonstrating sensitivity to change over 18 months (**Table S9**).

Table 1
Revision of mapping of ADCS-ADL-derived need for assistance to dependence score and projected care: ADCS-ADL Dependence Score algorithm (0-6).

0 Fully Independent	1 Mostly Independent	2 Moderately Independent	3 Mildly Dependent	4 Moderately Dependent	5 Mostly Dependent	6 Fully Dependent
No care needs	Informal visits/check-ins for those living alone	Limited in-home support	Frequent in-home support	Frequent and significant in-home support	Extensive in-home care or assisted living 1:1 care/nursing	24-hour care/supervision required (nursing facility or private residence)
Autonomous in all instrumental and basic ADLs	Reminders/ support for 1 or 2 iADLs only	Frequent reminders/ support for multiple iADLs	Assistance or physical help needed for 3 or more iADLS or only 2 iADLs and require support/reminders for bADLs	Significant assistance or physical help needed for 3 or more iADLS AND for 1 or more bADLs	Physical help needed for multiple bADLs	Reliant on others for basic needs (eating, walking, or toileting)

Abbreviations: ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ADL=Activities of Daily Living Inventory; bADL=basic ADL; iADL=instrumental ADL.

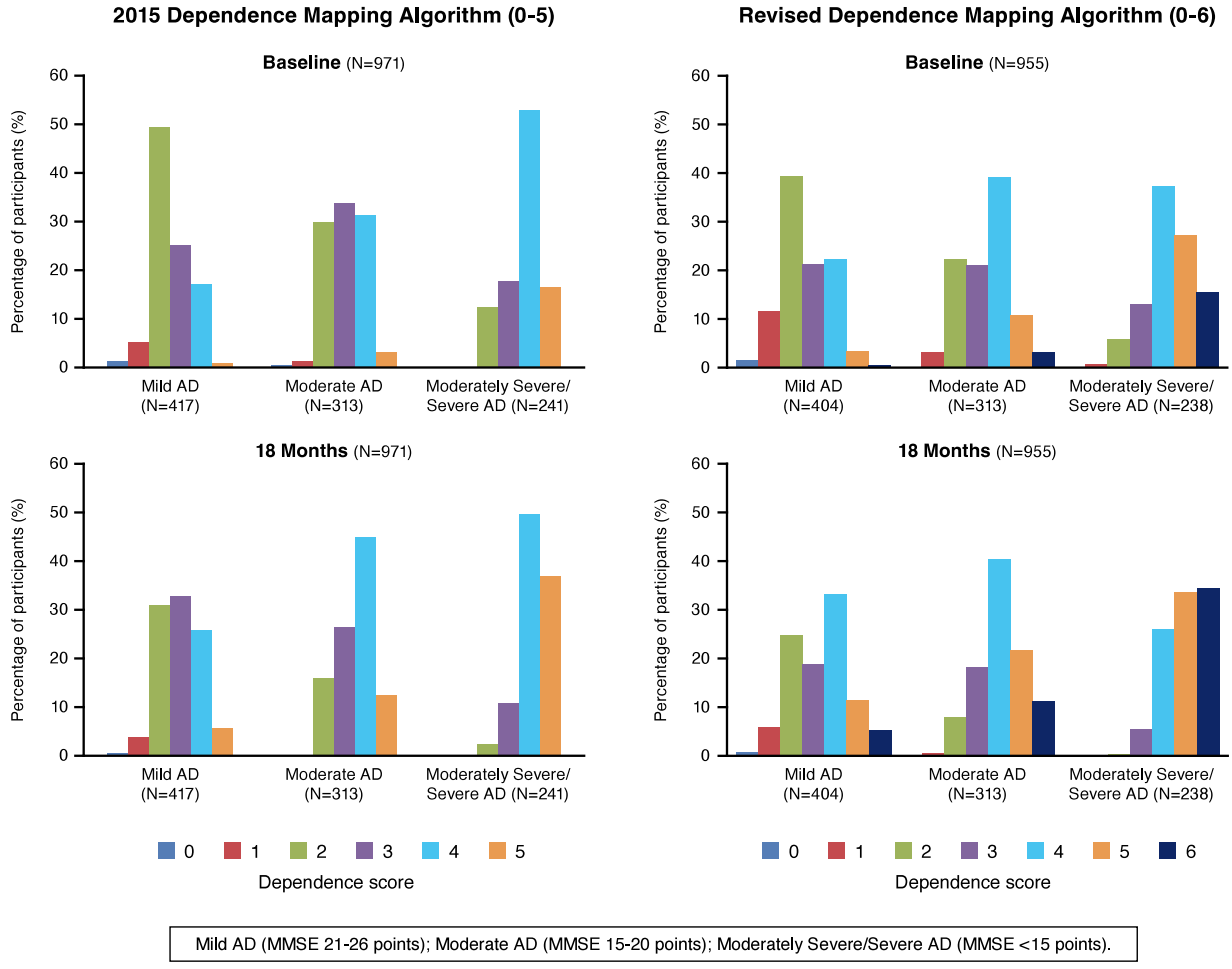

Fig. 1. Distribution of dependence by disease severity* at Baseline and 18 Months: GERAS-EU.
*Disease severity was defined using baseline MMSE.
Abbreviations: AD=Alzheimer's disease; DL=Dependence level; MMSE=Mini-Mental State Examination.

The revised algorithm showed stepwise increases in baseline dependence score associated with worse cognitive function (e.g., MMSE), neuropsychiatric symptoms (NPI-12), and care partner burden (ZBI), and increased care partner hours and total societal costs (Table 2). For example, individuals with a baseline dependence score of 1 had a mean MMSE of 22.5, whereas a dependence score of 5 was associated with worse cognitive function (MMSE of 12.5). Likewise, individuals with a baseline dependence score of 1 vs 5 was associated with a mean of 29.7 vs 318.9 care partner hours/month, respectively.

3.3.2. Clinical trial datasets

3.3.2.1. Distributions of dependence scores across AD severity and associations with clinical and economic outcomes. For pooled studies (EXPEDITION 1-3 and AMARANTH trials) in participants with MCI due to AD, and mild and moderate AD, expected distributions and shifts occurred from baseline to Month 18 across all levels of AD severity (Fig. 2A). At baseline, approximately 90% of participants with MCI due to AD and 80% of those with mild AD were either independent or moderately independent, with a dependence score of 0-2. In contrast, 72%

Table 2
Mean baseline clinical outcome scores by dependence score with revised ADCS-ADL Dependence Score algorithm (0-6): GERAS-EU.

Dependence score	# Patients (%Total) (N=1479)	MMSE Mean (95% CI)	ZBI Mean (95% CI)	NPI-12 Mean (95% CI)	Caregiver Time/Month (hr) Mean (95% CI)	Total Societal Costs (Monthly) (€) Mean (95% CI)	ADCS-ADL Mean (95% CI)	ADCS-bADL Mean (95% CI)	ADCS-iADL Mean (95% CI)
0	13 (0.9%)	24.5 (23.70, 25.38)	11.5 (8.47, 14.45)	4.5 (1.23, 7.85)	4.5 (-0.90, 9.98)	1248 (-582, 3079)	77.2 (76.38, 77.93)	22.0 (NA, NA)	55.2 (54.38, 55.93)
1	87 (5.9%)	22.5 (21.65, 23.37)	16.4 (14.39, 18.40)	6.7 (5.01, 8.35)	29.7 (19.18, 40.26)	703 (563, 843)	73.8 (73.13, 74.46)	21.8 (21.68, 21.96)	51.9 (51.28, 52.58)
2	314 (21.2%)	21.2 (20.82, 21.57)	21.5 (20.08, 22.82)	8.1 (7.15, 9.13)	65.7 (55.26, 76.10)	1064 (934, 1193)	66.1 (65.57, 66.63)	21.4 (21.28, 21.52)	44.6 (44.12, 45.14)
3	268 (18.1%)	19.3 (18.77, 19.87)	26.5 (24.87, 28.20)	12.8 (11.21, 14.30)	138.0 (119.20, 156.79)	1584 (1376, 1793)	54.0 (52.99, 54.97)	20.7 (20.48, 20.82)	33.2 (32.25, 34.18)
4	477 (32.3%)	16.6 (16.09, 17.07)	34.2 (32.87, 35.43)	17.0 (15.76, 18.22)	238.0 (221.20, 254.87)	2156 (1987, 2326)	39.8 (38.83, 40.84)	17.0 (16.81, 17.25)	22.8 (21.87, 23.62)
5	223 (15.1%)	12.4 (11.57, 13.19)	35.2 (33.25, 37.19)	21.8 (19.40, 24.21)	318.9 (293.33, 344.53)	3272 (2821, 3723)	25.2 (23.62, 26.78)	11 (10.56, 11.43)	14.2 (12.89, 15.47)
6	97 (6.6%)	9.4 (7.87, 10.94)	34.7 (31.66, 37.74)	28.6 (23.86, 33.39)	358.5 (317.96, 399.08)	3754 (3021, 4486)	15.8 (13.16, 18.47)	6.2 (5.24, 7.17)	9.6 (7.70, 11.40)

Abbreviations: ADCS=Alzheimer's Disease Cooperative Study; ADL=Activities of Daily Living Inventory; bADL=Basic Activities of Daily Living Inventory; CI=Confidence Interval; iADL=Instrumental Activities of Daily Living Inventory; MMSE=Mini-Mental State Examination; NPI-12=Neuropsychiatric Inventory-12; ZBI=Zarit Burden Interview.

of participants with moderate AD had a dependence score of 2-3. As the disease progressed, the proportion of participants exhibiting mild to full dependence (dependence score ≥3) increased across all AD severity stages. By Month 18, approximately 74% of participants with moderate AD were mildly to fully dependent. In the overall early symptomatic AD population for these pooled studies, a shift from dependence score 3 to dependence scores of 4-6 and from dependence score 4 to dependence scores of 5-6 was observed from baseline to 18 Months (**Table S10**). In addition, cognitive function (MMSE, iADRS), neuropsychiatric symptoms (NPI-12/NPI-Q), ADL, care partner burden, and care partner hours worsened with increasing dependence score at baseline (Table 3).

In the TRAILBLAZER-ALZ 2 study early symptomatic AD population with an MMSE of 20-28, most participants had dependence scores of 1-2 at baseline, with shifts to dependence scores of 2-5 over 18 months. Additionally, similar distributions and shifts occurred from baseline to Month 18 across all levels of AD severity for the TRAILBLAZER-ALZ 2 study (Fig. 2B). For this clinical trial, baseline cognitive function (MMSE, iADRS, ADAS-Cog13) and activities of daily living also worsened with increasing dependence scores using the revised ADCS-ADL Dependence Score algorithm (**Table S11**).

For the pooled CREAD I&II, GRADUATE I&II, and TAURIEL datasets, participants predominantly had dependence scores of 1 or 2 at baseline (Table 3). At 18 months, there was a shift toward higher dependence scores (Fig. 2C), with 50.5% of patients progressing over this period **(Table S12)**. At baseline, increased severity of cognitive impairment, functional impairment and neuropsychiatric symptoms were associated with higher dependence scores (Table 3). For the pooled GRADUATE I&II and TAURIEL studies, caregiver hours increased for dependence scores 2 to 4; the lack of an increase for dependence scores 5 and 6 is likely due to the very small sample size (Table 3). A similar pattern was observed at 18 months (**Table S13**).

Participants in the LAURIET study had higher dependence scores at baseline than those in the trials of early AD populations, given the inclusion of moderate AD patients in this sample, with half of patients assigned dependence scores of 3 and above (**Table S14**). By 12 months, 65% of participants had dependence scores of 3 and above (**Table S15**). Clinical outcomes worsened as dependence score increased at baseline (**Table S14**) and at 12 months (**Table S15**).

3.3.2.2. Relationship between dependence score and caregiver time by disease severity. For the GERAS-EU study, significant positive correlations were observed between caregiver time and dependence score at baseline (Pearson's r range: 0.269 to 0.605), Month 18 (Pearson's r range: 0.127 to 0.565), and change in baseline to Month 18 (Pearson's r range: 0.120 to 0.261) for all disease severity levels except for caregiver time for iADL and supervising for individuals with moderate AD (**Table S16**).

For the pooled EXPEDITION 1-3 and AMARANTH studies, significant positive correlations were found between caregiver time and dependence score stratified by disease severity (MCI due to AD, mild and moderate AD) at baseline (r ranging from 0.148 to 0.492), Month 18 (Pearson r range: 0.358 to 0.565), and change in baseline to Month 18 (Pearson's r range: 0.090 to 0.354) (**Table S17**).

3.3.2.3. Relationship between dependence score and key outcomes. The revised ADCS-ADL dependence score showed statistically significant correlations with all outcome measures (**Table S18**). In addition, results from linear regression analyses demonstrated that change in dependence score from baseline to Month 18 was significantly associated with changes in all key outcomes within the same time period ($p < 0.05$ for all; **Table S19**). These findings suggest that within participant increases in dependence score were closely linked to worsening of clinical outcomes.

4. Discussion

In 2015, Kahle Wrobleski et al developed an algorithm to map the item-level responses on the ADCS-ADL to "levels" of dependence and associated care needs using GERAS-EU study data from participants with mild-to-severe AD [9], which was subsequently validated using 18-month data [11]. However, the original dependence level algorithm [9] did not appear to accurately assign the "correct" dependence level to individuals with early symptomatic AD including those with MCI due to AD. The current work represents a collaborative effort to revise the original 2015 ADCS-ADL dependence algorithm [9] to expand applicability across all stages of AD severity, including those with early symptomatic AD. We refer to this revised algorithm as the ADCS-ADL Dependence Score. Overall, this work confirmed the validity of the ADCS-ADL Dependence Score algorithm across AD severities, leveraging a large cohort of individuals from historical clinical trials.

Across multiple datasets that included patients with MCI due to AD to moderate AD, we demonstrated that the distribution of dependence scores at baseline and shifts in dependence scores over 18 months increased with AD severity across all studies. Across measures, consistent, incremental worsening of mean outcomes was observed with each successive increase in dependence score from 0 to 5. Exceptions to this overall pattern observed in participants with dependence scores of 5 and 6 are likely attributable to the small number of participants contributing to these estimates. Furthermore, as dependence scores increased,

Table 3
Mean baseline clinical outcome scores by dependence score with revised ADCS-ADL dependence mapping algorithm (0-6).

Dependence score	# Participants (%Total)	MMSE Mean (95% CI)	iADRS Mean (95% CI)	ADAS-Cog13 Mean (95% CI)	ADCS-ADL Mean (95% CI)	ADCS-bADL Mean (95% CI)	ADCS-iADL) Mean (95% CI)	CDR-SB Mean (95% CI)	CDR-GS Mean (95% CI)	NPI-12/NPI-Q Mean (95% CI)	Caregiver Time (with no sleep time) / Month (hr) Mean (95% CI)
Pooled Lilly studies: EXPEDITION 1-3 and AMARANTH trials (N=1957)											
0	84 (4.3%)	25.0 (24.45, 25.52)	120.9 (119.48, 122.31)	22.3 (20.91, 23.67)	77.2 (76.85, 77.51)	19.0 (NA, NA)	58.2 (57.85, 58.51)	2.2 (1.89, 2.42)	0.5 (0.49, 0.54)	3.1 (2.12, 4.08)	22.5 (12.63, 32.33)
1	491 (25.1%)	24.0 (23.74, 24.21)	113.9 (113.17, 114.64)	25.8 (25.10, 26.45)	73.6 (73.42, 73.85)	19.0 (18.93, 18.97)	54.7 (54.47, 54.90)	2.7 (2.61, 2.82)	0.5 (0.52, 0.55)	4.4 (3.78, 4.96)	29.9 (24.61, 35.10)
2	961 (49.1%)	22.8 (22.59, 22.96)	103.4 (102.82, 104.05)	30.1 (29.62, 30.64)	67.4 (67.10, 67.65)	18.8 (18.73, 18.80)	48.6 (48.34, 48.88)	3.9 (3.77, 3.95)	0.7 (0.65, 0.69)	7.8 (7.18, 8.36)	68.9 (62.24, 75.50)
3	245 (12.5%)	21.7 (21.32, 22.10)	90.3 (88.91, 91.72)	33.4 (32.31, 34.42)	57.3 (56.52, 58.03)	18.6 (18.45, 18.66)	38.7 (37.97, 39.48)	5.1 (4.87, 5.33)	0.8 (0.79, 0.88)	11.1 (9.67, 12.50)	127.9 (108.41, 147.42)
4	148 (7.6%)	21.2 (20.69, 21.62)	82.1 (79.83, 84.27)	35.6 (33.97, 37.13)	49.3 (47.98, 50.57)	16.7 (16.44, 16.87)	32.6 (31.39, 33.81)	6.2 (5.83, 6.49)	1 (0.90, 1.04)	14.3 (12.15, 16.48)	193.2 (161.24, 225.08)
5	24 (1.2%)	20.9 (19.57, 22.26)	77.3 (69.06, 85.53)	38.8 (34.02, 43.56)	43.6 (37.90, 49.26)	12.5 (11.60, 13.31)	31.1 (25.72, 36.45)	7.8 (6.67, 8.99)	1.2 (0.92, 1.39)	12.5 (7.99, 16.93)	198.0 (107.08, 288.90)
6	4 (0.2%)	22.8 (19.22, 26.28)	98.00 (78.95, 117.05)	25.8 (12.93, 38.57)	52.3 (36.00, 68.50)	13.5 (9.71, 17.29)	38.8 (25.86, 51.64)	5.9 (2.41, 9.34)	0.9 (0.48, 1.27)	14.5 (-6.39, 35.39)	85.5 (-39.63, 210.53)
Pooled Roche Studies: CREAD, GRADUATE and TAURIEL trials (N=1893)*											
0	116 (6.1%)	24.92 (24.40, 25.44)	NA	24.50 (23.34, 25.66)	76.77 (76.43, 77.11)	18.97 (18.92, 19.01)	57.8 (57.46, 58.14)	2.57 (2.39, 2.75)	0.52 (0.50, 0.54)	1.48 (1.05, 1.90)	25.28 (7.92-42.64)
1	552 (29.2%)	24.35 (24.10, 24.60)	NA	25.87 (25.31, 26.43)	73.39 (73.17, 73.61)	18.96 (18.94, 18.98)	54.43 (54.21, 54.65)	2.88 (2.78, 2.98)	0.55 (0.54, 0.57)	2.01 (1.79, 2.23)	24.70 (17.75-31.65)
2	899 (47.5%)	23.16 (22.97, 23.36)	NA	29.18 (28.73, 29.63)	67.70 (67.43, 67.97)	18.78 (18.75, 18.82)	48.92 (48.65, 49.18)	3.88 (3.79, 3.98)	0.66 (0.65, 0.68)	3.29 (3.04, 3.55)	55.12 (47.10-63.13)
3	216 (11.4%)	22.66 (22.25, 23.07)	NA	31.68 (30.72, 32.64)	58.69 (57.92, 59.45)	18.52 (18.42, 18.62)	40.17 (39.40, 40.94)	4.70 (4.47, 4.93)	0.8 (0.76, 0.84)	4.21 (3.63, 4.79)	107.62 (83.99-131.25)
4	95 (5.0%)	21.72 (21.09, 22.35)	NA	34.48 (32.94, 36.03)	51.03 (49.36, 52.70)	16.81 (16.52, 17.10)	34.22 (32.70, 35.75)	5.64 (5.27, 6.01)	0.92 (0.86, 0.99)	6.09 (4.96, 7.22)	209.02 (156.30-261.75)
5	10 (0.5%)	23.00 (21.37, 24.63)	NA	33.00 (28.89, 37.11)	44.8 (38.41, 51.19)	13.50 (12.46, 14.54)	31.30 (25.34, 37.26)	6.55 (5.77, 7.33)	1.00 (1.00, 1.00)	2.89 (0.36, 5.42)	70.54 (12.11-128.97)
6	5 (0.3%)	23.00 (19.37, 26.62)	NA	28.40 (20.61, 36.19)	57.00 (53.26, 60.74)	14.6 (12.86, 16.34)	42.40 (39.33, 45.47)	5.20 (4.22, 6.18)	0.90 (0.70, 1.10)	3.40 (0.75, 6.05)	82.25 (-56.74, -221.24)

Abbreviations: ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS=Alzheimer's Disease Cooperative Study; ADL=Activities of Daily Living Inventory; bADL=Basic Activities of Daily Living Inventory; CDR-GS=Clinical Dementia Rating Scale – Global Score; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; CI=Confidence Interval; hr=Hour; iADL=Instrumental Activities of Daily Living Inventory; iADRS=Integrated Alzheimer's Disease Rating Scale; MMSE=Mini-Mental State Examination; NA=Not available; NPI-12=Neuropsychiatric Inventory-12; NPI-Q=Neuropsychiatric Inventory Questionnaire.

* For Roche studies, number of participants varied for each outcome, Caregiver time was only available for GRADUATE I & II and Tauriel studies, NPI-Q was only available for GRADUATE I & II and CREAD I & II studies.

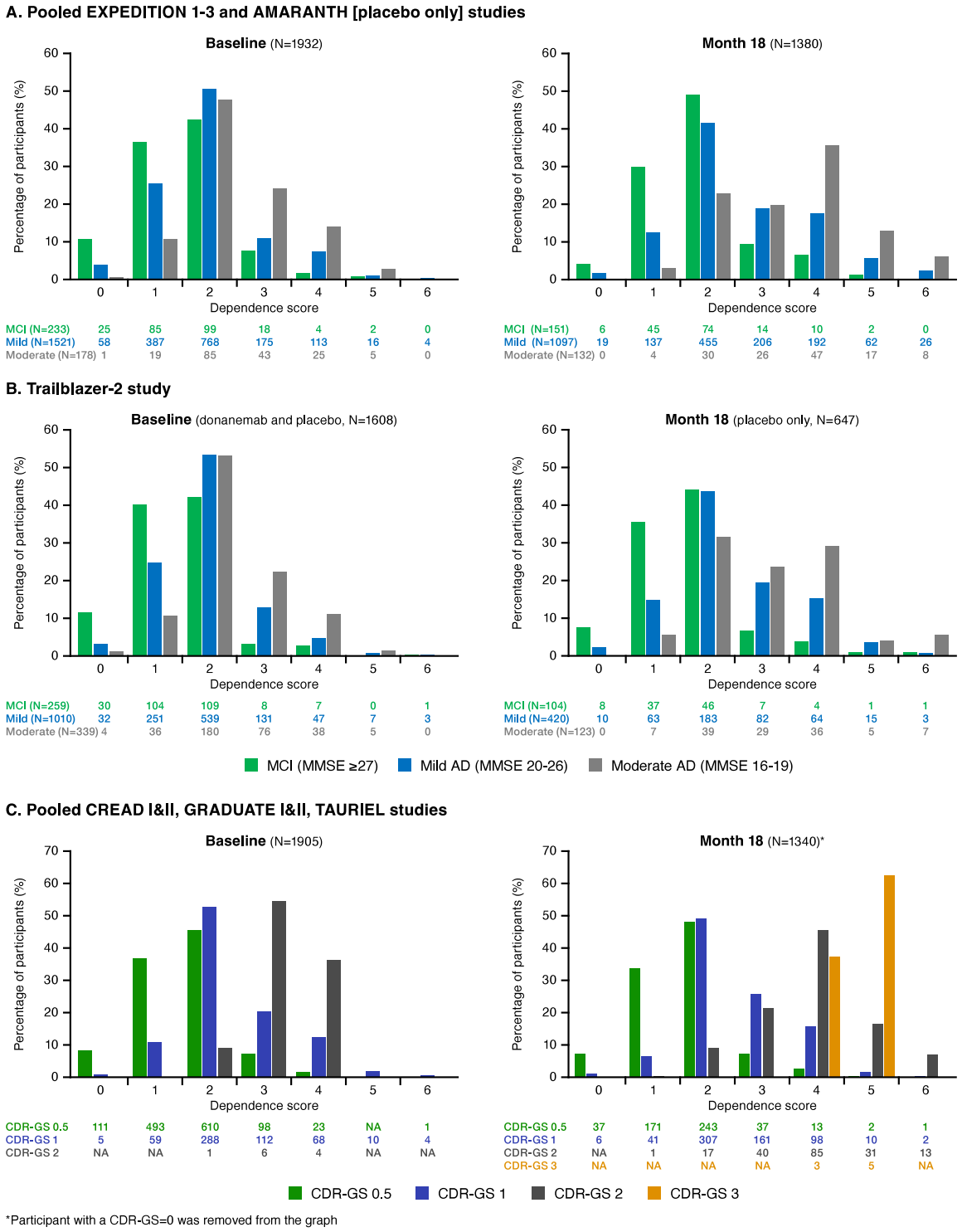

Fig. 2. Revised ADCS-ADL Dependence Score algorithm (0-6 levels) showing distributions at Baseline and over 18 Months by severity*
*Disease severity was defined using baseline MMSE or CDR-GS.
Abbreviations: AD=Alzheimer's disease; CDR-GS=Clinical Dementia Rating Scale – Global Score; DL=Dependence level; MCI=Mild cognitive impairment due to AD; MMSE=Mini-Mental State Examination; NA=Not available.

cognition and quality of life worsened, and neuropsychiatric symptoms (NPI-12/NPI-Q), caregiver burden (ZBI), and total societal costs (RUD-Lite) increased demonstrating that the dependence scores consistently reflected AD progression.

Compared to the original algorithm, the revised dependence scores showed stronger correlations with key clinical outcomes, indicating improved sensitivity and construct validity. Additionally, changes in the revised dependence scores were more responsive to shifts in clinical outcomes, further supporting their relevance. Instead of treating cognitive, functional, and behavioral changes as separate entities, the concept of dependence helps clinicians understand how these domains interact and contribute to the overall impact of AD [1].

Over the last several decades, many therapeutic strategies for AD have been explored and evidence supporting the clinical effectiveness

of some monoclonal antibodies directed at amyloid-β is emerging for early symptomatic AD (MCI due to AD and mild AD). Slowing of clinical progression in individuals with early symptomatic AD has recently been achieved with aducanumab, donanemab, and lecanemab [16,17, 35–36]. Understanding what slowing of disease progression means in terms of an individual's relative maintenance of independence offers additional context around the clinical meaningfulness of disease slowing, and is important to the individual with AD and their care partner. The revised ADCS-ADL Dependence Score algorithm described herein may offer a valuable approach to further translate the clinical relevance of novel therapies for AD. For example, one could assess the time to needing frequent in-home care (i.e., moving from a dependence score of 1 or 2 to a dependence score of 3 or greater). Delaying the time to needing frequent in-home care would indicate a maintenance of current level of independence for longer. Assessment of treatment group differences in the proportion of clinical trial participants who progress to a higher dependence score would also indicate a potential beneficial impact on independence.

4.1. Strengths and limitations

The main strengths of this analysis are the large number of individuals with AD included in the datasets and the robust validation steps undertaken. One key limitation is that the original ADCS-ADL was not developed to generate dependence scores. While individual items describe increasing levels of care support needed, response options are not consistent. As such, some judgments were required to calibrate the level of dependence across items. None of the datasets used in these analyses included the Dependence Scale [8]; thus, we were not able to compare the dependence scores from the algorithm to levels from Stern's Dependence Scale. A study with simultaneous administration of the Dependence Scale and the ADCS-ADL is needed to examine how well the ADCS-ADL Dependence Score algorithm aligns with the dependence levels identified by a validated score of dependence. Finally, while very few cases were excluded from the analyses due to either "Don't know" or missing responses (<2% of the study population), there is a potential for bias with the missing data rule.

4.2. Conclusions

These results support the use of the revised ADCS-ADL Dependence Score algorithm to assess dependence and supportive care needs across the AD severity continuum including individuals with early symptomatic AD. Results showed well-distributed dependence scores at baseline by AD severity (i.e., known-groups validity) that were consistent with expectations, responsiveness to change over 18 months, and strong correlation with other measures of disease progression (construct/convergent validity). Evaluating the benefits of new treatments for AD often involves assessment of changes in cognition and function (including ADCS-ADL); however, assessment of changes in dependence score and associated need for supportive care (i.e., progression to a higher dependence score, which impacts quality of life, care partner burden, health resource utilization, and cost) may provide a useful additional marker of drug efficacy. With the emergence of new treatments for early symptomatic AD, it is increasingly important to evaluate the clinical relevance of treatment effects in a variety of ways. The revised version of the ACDS-ADL Dependence Score algorithm presented herein provides a supplementary approach to understanding how treatments impact independence in individuals with AD and could be used in clinical trials where the ADCS-ADL has been administered but a direct measure of dependence has not been applied.

Funding support

This work (in kind support) was provided by Eli Lilly and Company and F. Hoffmann-La Roche Ltd.

Role of the funder/sponsor

The sponsors provided guidance for the conduct of the research and the preparation of the article; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the article for publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Julie M. Chandler was an employee of Eli Lilly and Company during the work for this manuscript.

Wenyu Ye, Mark Belger, and Alexandra S. Atkins are employees and minor shareholders of Eli Lilly and Company.

Xiaojuan Mi is an employee of TechData Services Company.

Claire J. Lansdall is an employee and minor shareholder of F. Hoffmann-La Roche AG.

Fiona McDougall and Balazs Toth are employees Genentech, Inc., a member of the Roche Group, and minor shareholders of F. Hoffmann-La Roche AG.

Kaycee M. Sink was an employee of Genentech, Inc., a member of the Roche Group, during the work for this manuscript. At the time of publication, she is a full-time employee of Cogstate, Inc., which had no role in the study. Kaycee M. Sink is a minor shareholder of F. Hoffmann-La Roche AG.

CRediT authorship contribution statement

Julie M. Chandler: Writing – original draft, Methodology, Writing – review & editing, Project administration, Conceptualization, Supervision, Investigation. **Claire J. Lansdall:** Writing – original draft, Formal analysis, Writing – review & editing, Investigation, Methodology, Conceptualization. **Wenyu Ye:** Methodology, Writing – original draft, Writing – review & editing, Formal analysis. **Fiona McDougall:** Writing – original draft, Conceptualization, Writing – review & editing, Data curation, Formal analysis. **Mark Belger:** Writing – original draft, Writing – review & editing, Formal analysis. **Balazs Toth:** Validation, Writing – review & editing, Formal analysis. **Xiaojuan Mi:** Validation, Writing – review & editing, Formal analysis. **Kaycee M. Sink:** Visualization, Writing – review & editing, Conceptualization. **Alexandra S. Atkins:** Visualization, Writing – original draft, Writing – review & editing, Conceptualization.

Acknowledgments

The authors thank Dr. Yaakov Stern for his consultation and critical review of the revised version of the ACDS-ADL Dependence Score alogrithm. Medical writing support was provided by Teresa Tartaglione, PharmD, of Certara Synchrogenix (funded by Eli LIlly and Company).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100261.

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