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RESEARCH ARTICLE

Assessing the clinical meaningfulness of slowing CDR-SB progression with disease-modifying therapies for Alzheimer's disease

Sarah M. Hartz[1] | Suzanne E. Schindler[2] | Marissa L. Streitz[2] | Krista L. Moulder[2] | Jessica Mozersky[3] | Guoqiao Wang[2,4] | Chengjie Xiong[4] | John C. Morris[2]

[1]Department of Psychiatry, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

[2]Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

[3]Department of Medicine, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

[4]Division of Biostatistics, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

Correspondence
Sarah M. Hartz, Department of Psychiatry, Washington University School of Medicine in St. Louis, 660 S. Euclid Ave, St. Louis, MO 63110, USA.
Email: hartzs@wustl.edu

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Abstract

INTRODUCTION: For many patients and caregivers, a major goal of disease-modifying treatments (DMTs) for Alzheimer's disease (AD) dementia is to extend independence in instrumental and basic activities of daily living (IADLs and BADLs). The goal of this study was to estimate the effect of treatments on the time remaining independent in IADLs and BADLs.

METHODS: Participants at the Knight Alzheimer Disease Research Center (Knight ADRC) who met eligibility criteria for recent DMT trials were studied: age ≥60 years at baseline, clinical diagnosis of very mild or mild AD dementia (global Clinical Dementia Rating [CDR] score 0.5 or 1), biomarker confirmation of amyloid pathology, and at least one follow-up CDR assessment within 5 years. For IADLs, a subset of the Functional Assessment Questionnaire (FAQ) was examined that rated the degree of independence in the following: paying bills, driving, remembering medications and appointments, and preparing meals. For BADLs, the Personal Care domain of the CDR was used. Mixed-effects logistic and ordinal regression models were used to examine the relationship between CDR Sum of Boxes (CDR-SB) and the individual functional outcomes and their components. The change in CDR-SB over time was estimated with linear mixed-effects models.

RESULTS: A total of 282 participants were followed for an average of 2.9 years (standard deviation [SD] 1.3 years). For 50% of individuals, loss of independence in IADLs occurred at CDR-SB >4.5 and in BADLs at CDR-SB >11.5. For individuals with a baseline CDR-SB = 2, treatment with lecanemab would extend independence in IADLs for 10 months (95% confidence interval [CI] 4–18 months) and treatment with donanemab in the low/medium tau group would extend independence in IADLs by 13 months (95% CI 6–24 months).

DISCUSSION: Independence in ADLs can be related to CDR-SB and used to demonstrate the effect of AD treatments in extending the time of independent function, a meaningful outcome for patients and their families.

KEYWORDS
clinical meaningfulness, AD dementia, functional independence

Highlights

- We estimated time to loss of independence for people with AD dementia
- Estimating time to loss of independence can help with clinical decision-making
- Disease-modifying treatments for AD dementia can extend independence

1 | INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by the cerebral accumulation of amyloid and tau pathology that causes synaptic and neuronal injury leading to progressive dementia. Recently, anti-amyloid monoclonal antibodies have been shown to reduce cerebral amyloid burden with corresponding slowing of the progression of AD dementia.[1,2] Based on these results, the U.S. Food and Drug Administration (FDA) approved lecanemab as a disease-modifying therapy (DMT) for early symptomatic AD in July 2023, and approved donanemab, also for early symptomatic AD, in July 2024. However, the degree to which these DMTs slow dementia progression is modest and has been deemed by some not to reach minimal clinical importance.[3] Given that therapy with these agents is costly, burdensome, and associated with risk for amyloid-related neuroimaging abnormalities (ARIA), there has been some reluctance to initiate treatment with these drugs without a clearer demonstration of their clinical benefit.[4]

Any AD treatment must show a clinically meaningful benefit that outweighs its risks and costs.[5] However, there is no consensus on what constitutes a "clinically meaningful" benefit for AD dementia.[6] Although it is generally agreed that cognition and functional performance should be assessed,[7–10] statistically significant differences in these scales in clinical trials may not always translate to a clinically meaningful effect as determined by the patient, their caregivers or family, and the treating clinician.[6] Complicating matters is that current trials of anti-amyloid monoclonal antibodies have been restricted to persons with very mild to mild symptomatic AD, in whom functional outcomes likely differ from those with moderate or severe AD dementia.

A common outcome measure for DMT clinical trials is the Clinical Dementia Rating scale (CDR®), a global scale to determine the presence or absence of dementia and, when present, its severity.[11,12] It assesses the influence of cognitive loss in six domains: three cognitive (Memory, Orientation, Judgment + Problem Solving) and three functional (Community Affairs, Home + Hobbies, Personal Care). Each of the six CDR domains are rated as unimpaired (0) or very mildly, mildly, moderately, or severely impaired (0.5, 1, 2, and 3, respectively). Summing the scores of the individual CDR domains or "boxes" yields the CDR-SB as a continuous measure, with scores ranging from 0 (no impairment in any domain) to 18 (severe impairment in all domains). A global CDR score is then derived from the individual domain box scores.[12] Individuals with a global CDR score of 0 are cognitively unimpaired, whereas individuals with a global CDR of 0.5 are very mildly impaired and those with global scores of 1, 2, and 3 are mildly, moderately, and severely impaired, respectively.

Patients and their families are typically most concerned with maintenance of independent function, which is highly related to safety and preservation of relationships.[13–16] Independent function can be quantified by measuring the ability to perform accustomed activities of daily living (ADLs). Instrumental ADLs (IADLs) vary for each person but often include financial management (e.g., paying bills), driving a motor vehicle or arranging other means of transportation, meal preparation, and remembering to take medications and keep appointments. Basic activities of daily living (BADLs) are essential self-care tasks that individuals perform themselves such as bathing, dressing, grooming, toileting, and eating.

The ability to perform IADLs and BADLs at an individual's accustomed level defines independence and is not only highly valued by patients and their families but also has significant financial implications. Indeed, in the United States, caregivers of people with AD who lost independent function provided an estimated 18 billion hours of unpaid assistance in 2022, valued at $339.5 billion.[17] In the United States, the average cost of residing in an assisted living facility is $56,068 per year, and the average cost of living in a nursing home is $112,556 for a private room and $98,534 for a shared room.[17] For these reasons, preservation of independence is a highly meaningful outcome for patients and their families.

Although studies of clinical meaningfulness in the context of DMTs have investigated the ADLs, CDR-SB, and time savings to clinically meaningful outcomes,[10,18–20] we sought an approach that would facilitate discussions between patients and providers regarding DMTs and how they may impact time to needing higher levels of care. This study aimed to connect a key outcome measure used by clinical trials (CDR-SB) to outcomes that are more likely to be meaningful to patients and their families (independence in ADLs). More specifically, we

estimated the number of months treatment with anti-amyloid monoclonal antibodies would be expected to prolong independence.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Although many studies have evaluated the clinical meaningfulness of global measures of Alzheimer's disease (AD) dementia progression, there has not been an integration of functional independence with global measures of AD dementia. The relevant studies are appropriately cited.
2. **Interpretation**: Our findings give a framework for contextualizing the Clinical Dementia Rating Sum of Boxes (CDR-SB) score for clinical decision-making with disease-modifying treatments (DMTs) of AD dementia.
3. **Future directions**: This article describes an approach to quantifying clinical meaningfulness of DMTs that facilitates discussions between patients and providers regarding time savings for needing higher levels of care and risks and benefits of DMTs for AD dementia.

2 | METHODS

2.1 | Participants

Community-living persons volunteered for participation in longitudinal studies at the Knight Alzheimer Disease Research Center (Knight ADRC) at Washington University. Both cognitively unimpaired and cognitively impaired participants were eligible for and agreed in principle to undergo amyloid positron emission tomography (PET) and lumbar puncture (LP) to obtain cerebrospinal fluid (CSF) for assays of amyloid beta (Aβ) and tau proteins, among other analytes. All participants underwent clinical and cognitive assessments using the Uniform Data Set (UDS),[21] which includes interviews with a study partner who knows the participant well (generally the spouse or other relative) to enable scoring of the CDR and the determination of the likely etiological diagnosis of the cognitive impairment, if present, in accordance with standard criteria.[21] Exclusion criteria for Knight ADRC participants include the inability to speak English and medical or psychiatric disorders that preclude longitudinal participation (e.g., dialysis for end-stage renal disease). For this study, we selected participants who met criteria similar to those enrolled in recent clinical trials of anti-amyloid antibodies[1,2]: participants had a clinical diagnosis of AD dementia in accordance with standard criteria with a global CDR score of 0.5 or 1 and confirmation of amyloid pathology as determined by CSF Aβ42/40 <0.0673[22] or amyloid PET Centiloid (CL) >20[23] within 1 year of the clinical AD diagnosis. In addition, all participants were 60 years of age or older at baseline and had at least one follow-up clinical assessment within 5 years of the baseline visit at which they were diagnosed with AD dementia. We used data from all assessments within this time period.

2.2 | Outcomes

The CDR-SB was used as a global measure for AD dementia progression.[11,12] IADLs were assessed with the Functional Activities Questionnaire (FAQ)[24] from the UDS in which the study partner rates the participant's current ability to perform accustomed activities relative to their previous ability to do so. The rating choices are: "performs normally" (scored as 0), "has difficulty but does it by themselves" (scored as 1), "requires assistance" (scored as 2), or "dependent" (scored as 3). In addition, there is an unscored "not applicable" category for participants who were unaccustomed to doing a particular activity. Based on studies of outcomes of interest to patients and their caregivers,[15,16] we selected 4 of the 10 activities in the FAQ as indicative of activities that represent independent living: (1) managing personal finances (e.g., paying bills, keeping financial records), (2) driving a motor vehicle or arranging travel outside of the home, (3) remembering to take medications and to keep appointments, and (4) preparing a balanced meal. We defined loss of independence in IADLs as a score of 2 ("requires assistance") or 3 ("dependent") in at least three of the four activities. For BADLs, we used the CDR Personal Care domain,[11] with loss of independence in BADLs defined as a score of 2, indicating "requires assistance in dressing, hygiene, keeping of personal effects"; or 3, indicating "requires much help with personal care."

2.3 | Statistical Modeling

All statistical analyses used SAS 9.4[25] and/or R version 4.4.0.[26] To model CDR-SB progression over time we used the hlme function of the R lccm package,[27] estimating a linear mixed model (without intercept) on the change in CDR-SB from baseline (time = 0) as a function of time, with random effects on slopes for individual participants. In a second model, baseline CDR global score (0.5 or 1) was included as a categorical variable interacting with time.

To model the relationship between CDR-SB and each functional outcome, we selected participants without impairment in the outcome at the baseline assessment (i.e., different subsamples were used for each outcome). IADLs and BADLs were coded as dichotomous variables, and the four FAQ items (personal finances, driving, remembering meds/appointments, and meal preparation) were coded as ordinal variables. For each functional outcome, we fitted generalized linear mixed-effects models to CDR-SB with participant-level random effects. The glmer function of the lme4 R package[28] was used to fit dichotomous outcomes. We ran ordinal logistic regression for the ordinal outcomes using the mixed_model function of the GLMMadaptive R package.[29] For independent IADLs and BADLs, we used the regression models to identify the first CDR-SB where 50% of participants

TABLE 1 Participant characteristics.

	Full sample	Baseline CDR 0.5	Baseline CDR 1
Participants	282	188	94
Visits	821	587	234
Age in years at baseline	74.8 (6.8)	74.5 (6.8)	75.4 (7.0)
Gender			
Female	123 (44%)	77 (41%)	46 (49%)
Male	159 (56%)	111 (59%)	48 (51%)
Race			
Black or African American (non-Hispanic)	28 10%	12 (6%)	16 (17%)
White (non-Hispanic)	249 (88%)	172 (92%)	77 (82%)
Hispanic ethnicity or other race	5 (2%)	4 (2%)	1 (1%)
Average years of education	15.1 (3.1)	15.4 (3.0)	14.2 (3.2)
Average number of years observed	2.9 (1.3)	3.1 (1.3)	2.3 (1.3)
Average CDR-SB at baseline	3.6 (1.8)	2.6 (1.0)	5.7 (1.2)
Independent Instrumental ADL[a]	127 (45%)	102 (54%)	25 (27%)
Independent Basic ADL[b]	281 (100%)	188 (100%)	93 (99%)
Biomarker used for diagnostic confirmation			
Amyloid PET	43%	46%	37%
Amyloid PET Centiloid	58 (45)	56 (45)	62 (48)
CSF biomarkers	57%	54%	63%
Lumipulse Aβ42/Aβ40 (ratio)	0.044 (0.009)	0.043 (0.008)	0.045 (0.009)
Estimated annual increase in CDR-SB (95% CI)	1.30 (1.12, 1.48)	1.06 (0.85,1.26)	1.85 (1.70, 2.00)

For categorical variables, counts and percentages are provided. For continuous variables, the mean and standard deviation are provided.
[a]Scored as "independent" or "has difficulty" on ≥3 of 4 FAQ items (meal prep, driving, remembering appointments/medications, personal finances).
[b]CDR Personal care box score ≤1.

were predicted to be dependent (referred to as cutoffs for IADLs and BADLs).

To estimate the time (and corresponding 95% confidence intervals [CIs]) to the CDR-SB values associated with loss of independence in IADLs or BADLs, we adapted a model for estimation of time savings in AD treatment trials.[30] Specifically, we used the statistical models of the association between time (*x*-axis) and CDR-SB (*y*-axis) from our modeling and converted them to estimate CDR-SB as a function of time with corresponding CIs. For clinical trial data, we used an analogous approach to estimate time to a CDR-SB cutoff for the placebo and treatment groups based on the published changes in CDR-SB.[1,2]

3 | RESULTS

3.1 | Participant characteristics

Of the 282 participants who met the inclusion criteria, 67% had very mild AD dementia (CDR 0.5) and 33% had mild AD dementia (CDR 1) (Table 1). The sample overall was 88% non-Hispanic White and 10% Black or African American. Slightly more participants were men (56%). Most participants were well educated, with an average of 15.1 years of education. The 282 participants were followed for an average of 2.9 years (participants who progress to CDR 2 or greater no longer are assessed with the UDS).

3.2 | Relationship between IADLs, BADLs, and CDR-SB

For IADLs at baseline, most CDR 0.5 participants (95%) were independent, whereas a minority of CDR 1 participants (40%) were independent (Table 1). Nearly all participants were independent in BADLs at baseline. We individually modeled the four individual components of IADLs (paying bills, driving, remembering medications/appointments, and meal preparation) and estimated the level of independence for each of the four items as a function of the CDR-SB score (Figure 1A). There were differences between the four components in the estimated CDR-SB score at which an estimated 50% of participants were dependent. For example, participants remained independent in meal preparation and remembering medication/appointments at a higher CDR-SB as compared to paying bills and driving.

We next examined the relationship between CDR-SB and loss of independence in ADLs. Independence in IADLs, as defined by loss

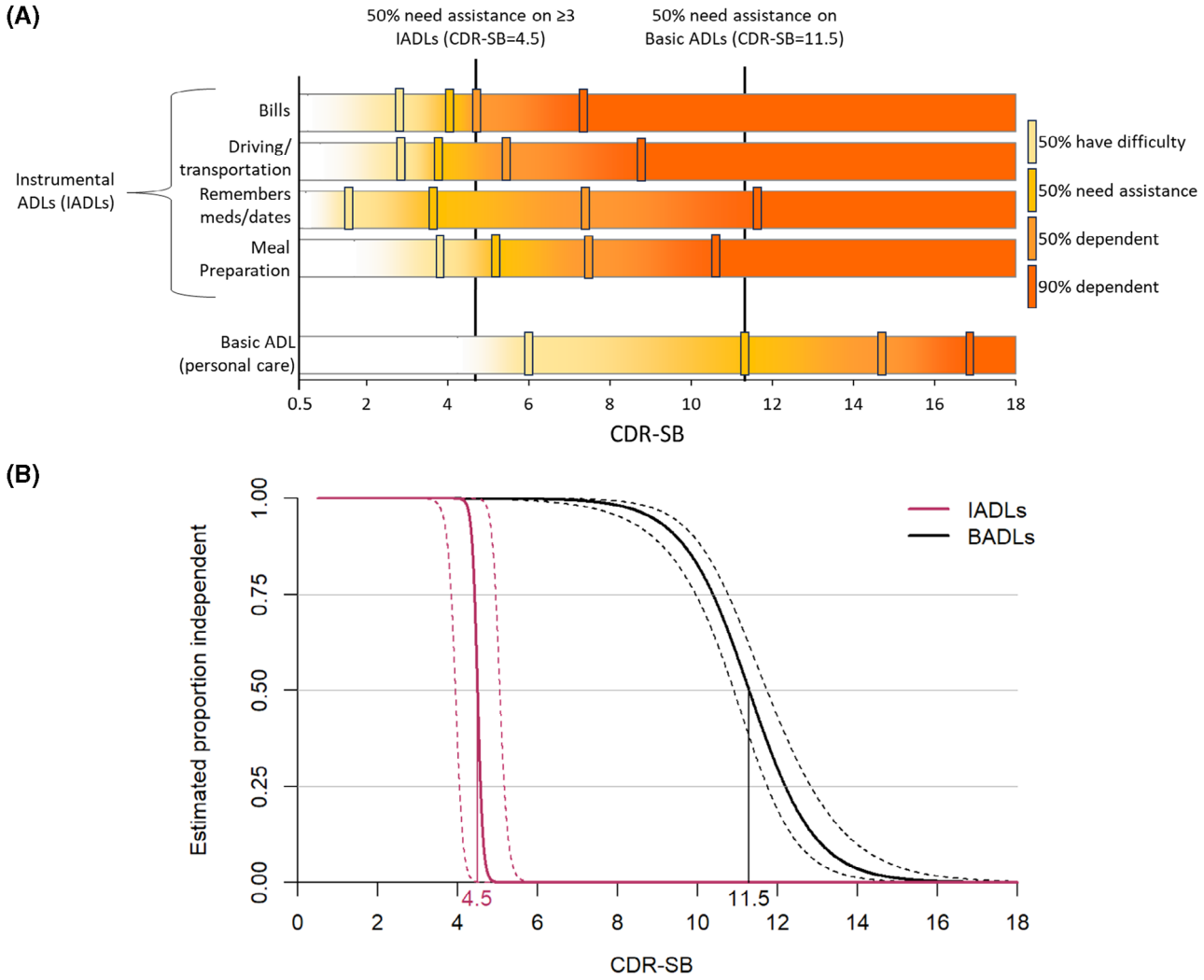


FIGURE 1 Relationship between CDR-SB and functional outcomes. (A) shows the decline in components of ADLs: IADLs (personal finances, driving, remembering appointments/medications and meal preparation, with non-independence defined as "needing assistance" or "dependent" on at least three of these), and BADLs (including dressing and personal hygiene). (B) Shows the probability of independence in IADLs and BADLs relative to CDR-SB. Dashed lines represent boundaries for 95% confidence intervals. The CDR-SB score is noted where an estimated 50% of participants are no longer independent in ADLs. ADLs, activities of daily living; BADLs, basic ADLs; CDR-SB, Clinical Dementia Rating Sum of Boxes; IADLs, instrumental ADLs.

of independence with three or more of the four IADLs components, occurred at CDR-SB = 4.5 for 50% of individuals (Figure 1B, based on *N* = 352 visits from *N* = 127 participants with independent IADLs at baseline). Loss of independence in BADLs, as defined by requiring assistance with personal care, occurred at CDR-SB = 11.5 for 50% of individuals (based on *N* = 884 visits from *N* = 285 participants with independent BADLs at baseline). Both threshholds had very high concordance, highlighting the strong relationship between CDR and ADLs. For BADLs, 93% of participant visits scored as CDR-SB <4.5 were also scored as independent in IADLs and 87% of visits with CDR >4.5 did not have independence in IADLs (47% of those with CDR-SB = 4.5 had independence in IADLs). Similarly, 97% of participant visits scored as CDR-SB <11.5 were also scored as independent in BADLs and 85% of observed visits with CDR-SB >11.5 did not have independence in BADLs (no participants scored CDR-SB = 11.5).

3.3 | Estimating remaining time of independence

The first step in estimating remaining time of independence in ADLs was to model progression of CDR-SB over time (change from baseline CDR-SB, Table 1). Overall, the average annual CDR-SB increase was 1.30 (95% CI 1.13–1.48). When modeled as a function of baseline CDR, CDR-SB increased by 1.05/year (95% CI 0.85–1.26) for individuals with a baseline CDR 0.5 and by 1.85/year (95% CI 1.70–2.00) for individuals with a baseline CDR 1. Of note, although different slopes are estimated for the different baseline CDR global values, the model assumes a linear increase in CDR-SB over time.

The modeled rate of increase in CDR-SB was then used to estimate the remaining time of independence in IADLs and BADLs. First we estimated the CDR-SB over time for each baseline CDR-SB (Figure 2A). Next, for each baseline CDR-SB value we estimated the time to loss

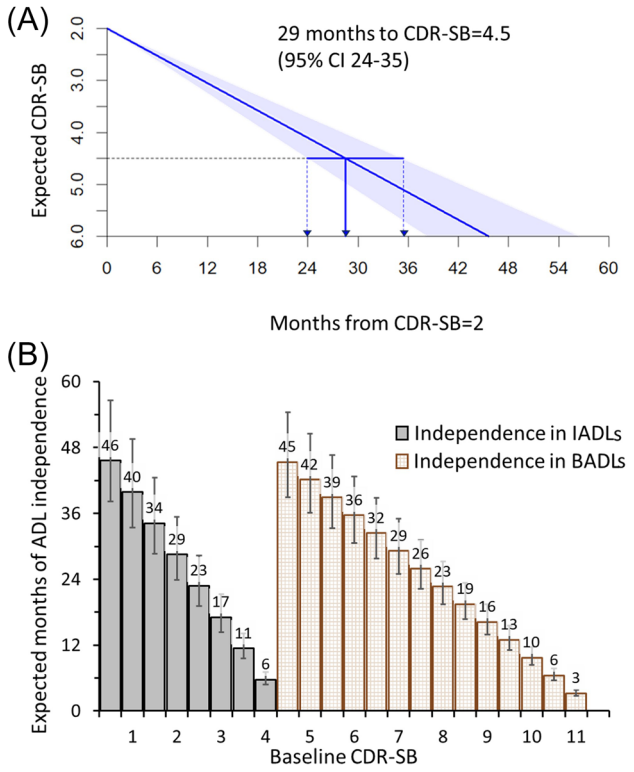


FIGURE 2 Translation of CDR-SB progression to estimated time remaining with independence in ADLs. (A) Illustrates the computation of expected months of independence in IADLs (CDR-SB = 4.5) for baseline CDR-SB = 2, using the estimated annual change in CDR-SB shown in Table 1. (B) Expands this calculation to baseline CDR-SB 0.5–11, showing the estimated months remaining of independence in IADLs (time to CDR-SB = 4.5) for global CDR 0.5 (baseline CDR-SB 0.5–4), and independence in BADLs (time to CDR-SB = 11.5) for global CDR 1 (baseline CDR-SB 4.5–11). ADLs, activities of daily living; BADLs, basic ADLs; CDR-SB, Clinical Dementia Rating Sum of Boxes; IADLs, instrumental ADLs.

of independence in IADLs (time to CDR-SB = 4.5) and BADLs (time to CDR-SB = 11.5), with the corresponding CIs (Figure 2B). For example, an individual with a baseline CDR-SB = 2 (with a corresponding global CDR 0.5) is estimated to have an annual increase in CDR-SB of 1.05, with a 95% CI of 0.85–1.26 (Figure 2A). Based on this, the expected time to loss of independence in IADLs (CDR-SB = 4.5) is 29 months (95% CI 24–35 months). We made analogous computations for each baseline CDR-SB, computing remaining time of independence in IADLs for baseline CDR-SB <4.5 and remaining time of independence in BADLs for baseline CDR-SB <11.5 (Figure 2B). This assumes linear rates of change that are constant within global CDR 0.5, and constant within global CDR 1.

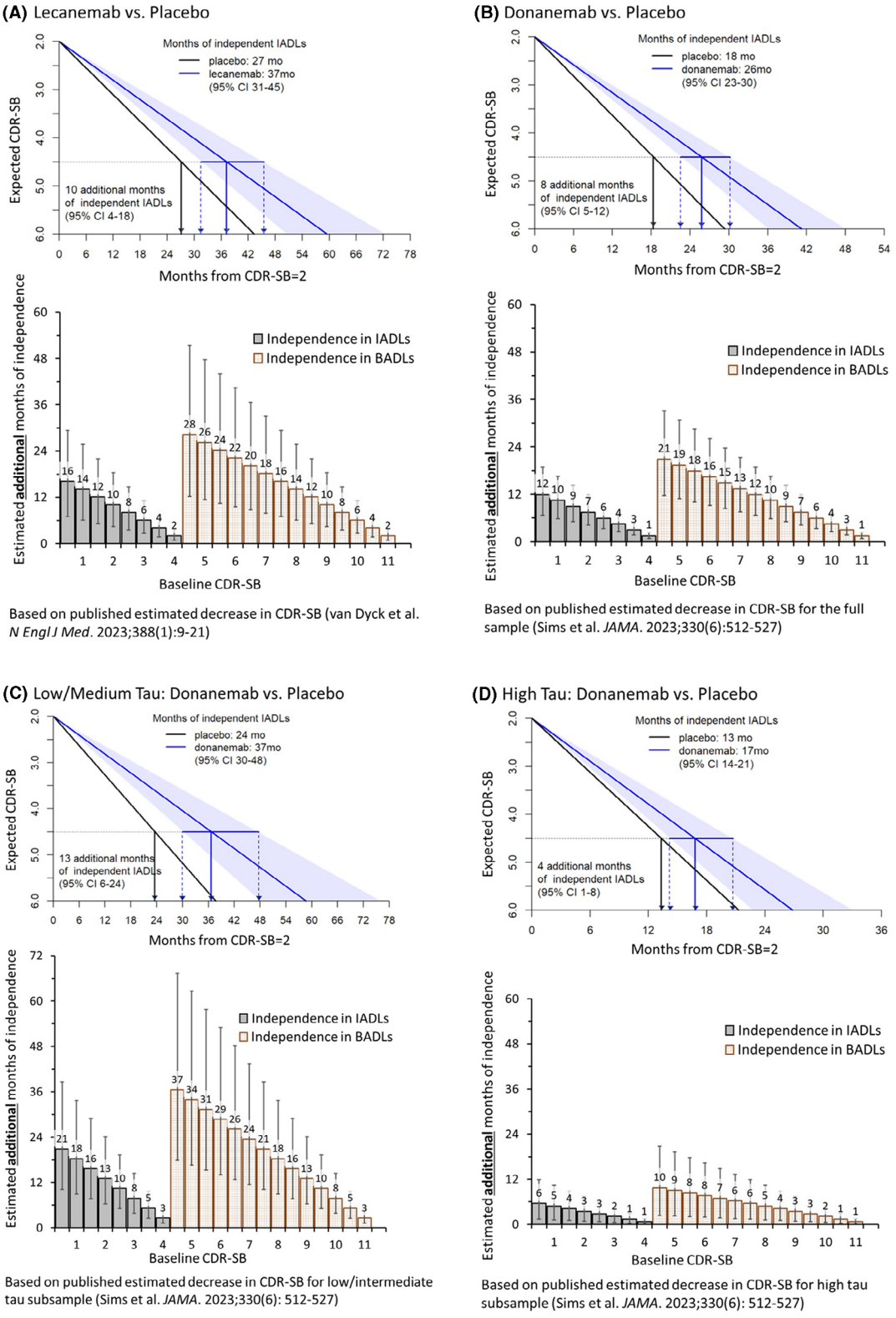
Finally, we estimated the additional years of independence in IADLs and BADLs associated with lecanemab treatment or donanemab treatment due to the slower rate of decline in CDR-SB (Figure 3). To do this, we assumed that disease progression in each arm (placebo and treatment) was linear both during and after the trial period, with a slope based on the observed effect at the end of the trial. The lecanemab trial found an average annual progression in CDR-SB for the placebo group of 1.11 (based on the published 18-month ΔCDR-SB of 1.66), with treatment decreasing this progression by 0.3 (95% CI 0.15–0.45, based on the published 18-month decrease in ΔCDR-SB by 0.45).[1] Assuming these effects are constant over the course of treatment, those with baseline CDR-SB = 2 would be expected to have an additional 10 months of independence in IADLs on lecanemab (95% CI 4–18 months, Figure 3A).

Similarly, the donanemab trial found an average annual progression in CDR-SB for the placebo group of 1.65 (based on the published 76-week ΔCDR-SB of 2.42), with treatment decreasing this progression by 0.48 (95% 0.31–0.65, based on the published 76-week decrease in ΔCDR-SB of 0.7) in the combined population.[2] The donanenab trial also reported a differential effect of treatment based on the measured tau PET levels: among those with low/medium tau PET, the placebo group had an average annual CDR-SB progression of 1.29, with donanemab decreasing progression by 0.46 (95% CI 0.27–0.65), and among those with high tau PET, the placebo group had an average annual CDR-SB progression of 2.29 with donanemab treatment decreasing progression by 0.47 (95% CI 0.140.82). Assuming that these effects are constant over the course of treatment, those with baseline CDR-SB = 2 if treated with donanemab would be expected to have an additional 8 months of independence in IADLs (95% CI 5–12 months, Figure 3B) in the combined population, an additional 13 months of independence in IADLs for the low/medium tau PET group (95% CI 6–24, Figure 3C), and an additional 4 months of independence in IADLs– for the high tau PET group (95% CI 1–8 months, Figure 3D).

4 | DISCUSSION

To better understand whether anti-amyloid treatments have a clinically meaningful benefit, we examined the relationships between the CDR-SB and functional independence, an outcome important to patients and families. In a cohort of individuals diagnosed with early AD dementia who were confirmed to have amyloid pathology, we found that a loss of independence in IADLs occurs at CDR-SB >4.5 and in BADLs occurs at CDR-SB >11.5. We examined the rate of annual decline in CDR-SB, and then estimated the time to loss of independence in IADLs (time until CDR-SB = 4.5) and BADLs (time until CDR-SB = 11.5). Finally, using published estimates quantifying the effects of anti-amyloid treatments on slowing decline in the CDR-SB, we estimated how long anti-amyloid treatments are expected to extend independence in IADLs and BADLs.

The time to independence in ADLs is related to the baseline functioning, and therefore additional time of independence in ADLs attributable to DMT varies. For example, an individual with a baseline CDR-SB of 2 (typically fully independent in BADLs, independent in IADLs but may have difficulty with remembering dates and medications) could expect around 10 additional months of independence in IADLs on lecanemab (95% CI 4–18 months) and 13 months of independence on donanemab (95% CI 6–24), assuming they have low/medium tau PET at baseline. In contrast, an individual with a baseline CDR-SB of 3.5 (typically fully independent in BADLs, independent in IADLs but may have difficulty with remembering dates and medications, paying



Based on published estimated decrease in CDR-SB (van Dyck et al. *N Engl J Med*. 2023;388(1):9-21)

Based on published estimated decrease in CDR-SB for the full sample (Sims et al. *JAMA*. 2023;330(6):512-527)

Based on published estimated decrease in CDR-SB for low/intermediate tau subsample (Sims et al. *JAMA*. 2023;330(6): 512-527)

Based on published estimated decrease in CDR-SB for high tau subsample (Sims et al. *JAMA*. 2023;330(6): 512-527)

FIGURE 3 Example computation of estimated months of independence in ADLs saved by DMTs using published results. (A) Shows results of the lecanemab trial. (B–D) Show results of the donanemab trial: the full sample results are in B, and then the results are partitioned into (C) low/medium tau and (D) high tau. ADLs, activities of daily living; DMTs, disease-modifying treatments.

bills, and driving) could expect around 4 additional months of independence in IADLs on lecanemab (95% CI 2–7 months) and 5 months of independence on donanemab (95% CI 2–9 months) for those with low/medium tau PET. This interpretation of clinical meaningfulness of treatment will be particularly important for clinical decision-making, allowing for personalized estimates of time to independence (based on baseline CDR-SB and, potentially, tau PET levels) that can be weighed against an individual's risks of treatment.

Relating the CDR-SB, a global measure of AD dementia severity used in clinical trials, to independence in IADLs and BADLs can help patients and their families understand the benefit of treatment. The course of AD dementia from symptom onset to death generally occurs over 7–10 years,[31] making the effects of treatment more difficult to understand when trials occur over a relatively short period (18 months). The issue of how long to treat with DMTs remains unresolved. It is very difficult to know whether treatment effects will persist past the clinical trial period, although it has been noted that the treatment effect of lecanemab seemed to increase with duration of treatment.[1]

The slowness of AD dementia progression may magnify the potential impact of DMTs on quality of life and health care costs. For example, a modest slowing of disease progression as seen in the lecanemab trial could translate into an additional year of independent living for those starting with CDR-SB = 1, or 9 months of independent living for those starting with CDR-SB = 2. Delaying a move to an assisted living facility, with an average yearly cost of $56,068,[17] could result in a significant savings to patients and families.

It is important to note that there are methodological limitations to our study. First, to maximize the quality of our data, we limited the sample to Knight ADRC participants with biomarker-confirmed AD dementia and available longitudinal clinical data within 5 years. This restricted both our sample size and our sample demographics, potentially limiting the generalizability of the results from the highly engaged longitudinal research cohort with biomarker-confirmed AD to a general population. Of note, we did not exclude participants with clinically significant magnetic resonance imaging (MRI) lesions suggestive of vascular or other non-AD causes of dementia. This is similar to the donanemab trial[32] but differs from the lecanemab trial.[33] Second, we assumed that CDR-SB progression is linear and that treatment effects occur uniformly during the observed study period, and that they extend at the same linear rate beyond the length of the study. Based on other studies,[34] cognition declines in a "waterfall" shape, suggesting that early reduction of decline may have even greater benefits at later time points. Third, we did not directly investigate the loss of function in ADLs as a function of time but rather related ADLs to CDR-SB and modeled time until a CDR-SB value associated with loss of function. Although this enabled us to model treatment effects that were reported in CDR-SB, this is an indirect analysis. Future studies should explore direct associations between time and loss of ADLs and confirm estimated inflection points in different samples to ensure robustness.

Despite the methodological limitations of our study, these findings can serve as a tool for understanding the relationship between the CDR-SB and functional independence. Our hope is that this modeling can be used to describe the functional implications of AD dementia progression, regardless of whether amyloid-lowering treatments are being considered. Furthermore, this work provides an approach to better understand the clinical meaningfulness of AD treatments in terms that patients and families may find more understandable.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided written informed consent.

ORCID

Sarah M. Hartz https://orcid.org/0000-0002-5429-3799

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SUPPORTING INFORMATION

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

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