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Original Research

Potential Implications of Slowing Disease Progression in Amyloid-Positive Early Alzheimer's Disease: Estimates from Real-World Data

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Abstract

BACKGROUND: Emerging therapies have shown promising results for slowing the progression of Alzheimer's disease (AD). However, the potential impact of these therapies on real-world outcomes remains to be explored.

OBJECTIVE: To examine the impact of slowing AD progression on functional abilities and behavioral symptoms.

DESIGN: Retrospective observational study.

SETTING: Data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) in the United States (06/2005-11/2021, primary analysis) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (09/2005-03/2022, sensitivity analysis) were used.

PARTICIPANTS: Individuals with mild cognitive impairment (MCI) or mild dementia, Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score 0.5-9.0 (inclusive; first visit defined as the index date), and confirmed amyloid positivity were identified in NACC. In ADNI, individuals with at least one clinical center visit with a clinical assessment of MCI or mild dementia and confirmed amyloid positivity were identified.

MEASUREMENTS: Hypothetical effects of slowing disease progression as assessed by CDR-SB on functional and behavioral outcomes including the Functional Activities Questionnaire (FAQ) score, Neuropsychiatric Inventory Questionnaire (NPI-Q) score, and the probability of complete dependence over five years were evaluated using multivariable regression among NACC participants, separately for the subgroups with MCI and mild dementia at baseline, respectively. For the ADNI sensitivity analysis, the hypothetical effects of slowing disease progression were evaluated for FAQ score using multivariable regression among the MCI participants only.

RESULTS: Compared with natural disease progression, slowing progression by 20% over five years for NACC participants with MCI and mild dementia, respectively, would result in 1.7-point (10.8%) and 1.6-point (12.9%) less deterioration based on FAQ; 0.5-point (20.3%) and 0.5-point (19.3%) less deterioration based on NPI-Q; 4.7 percentage-point (22.2%) and 10.1 percentage-point (21.6%) lower probability of complete dependence. Among ADNI participants, delaying disease progression by 20% or 30% over 4 years would avert deterioration based on FAQ of 1.1 points (20.4%) and 1.6 points (29.6%), respectively, compared to natural disease progression.

CONCLUSIONS: Slowing early AD progression could result in preservation of functional and behavioral attributes and functional autonomy for longer.

Key words: Alzheimer's disease, mild cognitive impairment, beta amyloid, disease progression, clinical outcomes

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, affecting an estimated 6.2 million Americans over age 65 (1, 2). Given the aging population, this number is projected to increase to 13.8 million by 2060 (1). While there is still no consensus on the etiology and pathophysiology of AD, current disease models highlight the importance and interaction of plaque-forming amyloid-β (Aβ) peptides and tau proteins in the brain that are correlated with disease progression and symptom severity (3, 4). As AD progresses in severity, the associated clinical, humanistic and economic burden rises. Current estimates of economic burden of AD in the US, including direct and indirect medical costs, indicate annual costs of AD amount to approximately $305 billion (5). Further, AD is currently ranked as the sixth leading cause of death among US adults, and 5th among adults over age 65 (6). Despite the large clinical burden, there are currently limited effective treatment options for AD. The majority of medications approved by the US Food and Drug Administration (FDA), such as cholinesterase inhibitors and the N-Methyl-D-Aspartate (NMDA) receptor antagonist memantine, only treat symptoms and do not address the underlying pathology of AD (1). Aducanumab and lecanemab are the first FDA-approved disease-modifying treatments for AD, having shown potential in reducing amyloid plaque levels in clinical trials (5, 6); however, the real-world implications of these treatments, particularly over longer time horizons, are currently unknown. A better understanding of the long-term outcomes associated with differential rates of disease progression earlier in the disease trajectory among individuals with biomarker-confirmed early, symptomatic AD may provide insights into potential benefits that could be realized over time from emerging disease-modifying treatments for AD.

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There is currently no cure for AD, nor any definitive evidence-based recommendations for prevention, and treatments typically provide only symptomatic relief. Recently, the FDA provided accelerated approval for two anti-Aβ monoclonal antibodies with disease modifying potential among individuals with early AD – Aduhelm® (aducanumab) (7) and Leqembi® (lecanemab), with lecanemab being granted traditional approval upon conclusion of the Phase 3 CLARITY AD trial (8-10). Aducanumab was shown to reduce Aβ plaque with a concomitant decrease in the rate of cognitive decline over 76 weeks in one phase 3 trial (EMERGE), but with no evidence of cognition-sparing effects in another, identically designed phase 3 trial (ENGAGE) (11). Lecanemab was associated with a moderate (27%) reduction in disease progression over 18-months (as measured by changes in Clinical Dementia Rating® Dementia Staging Instrument Sum of Boxes (CDR-SB) compared to placebo (8, 9, 12). Clinical trials for other emerging therapies have also shown promising results. For instance, donanemab (currently under regulatory review), is an antibody that targets a modified form of deposited Aβ peptide in the brain and has shown the potential to reduce disease progression as assessed by changes in CDR-SB by 29% for Alzheimer's disease in the earliest, symptomatic stages, with better scores for cognition and daily functioning at 76 weeks in clinical trial participants with early AD, compared to placebo (13, 14).

In view of continuing advances in modern treatments, there is growing interest in assessing the potential impact of slowing AD progression on clinical, economic, and humanistic outcomes for individuals diagnosed at early stages of the disease continuum. Recent studies have investigated the potential economic benefits attributable to slowing disease progression. Using data from the GERAS-UK study, Lenox-Smith et al. (2018) reported that a 3.6-point reduction in the Mini-Mental State Examination (MMSE) score (indicating worsening cognition) among people with early AD was associated with an 8.7% increase in total societal costs (increase of over £2,200) per person over the 18-month period of assessment (15). Reducing the decline in cognitive ability in AD by 30% was associated with a comparatively lower increase of £670 per person with early AD, mostly attributable to indirect cost reductions in caregiver time and informal care (15). Results from the GERAS-EU (France, Germany and UK) study of community-dwelling AD dementia participants and their caregivers similarly showed that informal caregiver time was the cost driver for total societal costs at each level of AD dementia severity, accounting for 54–65% of the 18-month costs (16). In another study combining the GERAS cohort and four randomized clinical trials and including patients with mild cognitive impairment (MCI), mild AD, and moderate AD, the 18-month change on the integrated Alzheimer's Disease Rating Scale (iADRS) was significantly associated with changes in patient cognitive and functional outcomes, quality of life, as well as economic costs and caregiver burden (17). In the MCI cohort from the longitudinal GERAS-US cohort study conducted between 2016 and 2021, a 2.1-point worsening in MMSE over 36 months was associated with a cumulative increase of 35.7 hours (95% confidence interval [CI]: 25.2, 46.1) in total caregiver time, with an associated increase in total societal cost of $8,084 per patient (95% CI: $1,091, $15,637) (18). Slowing disease progression by 30% (equivalent to 1.7-point decrease in MMSE) predicted a relative decrease in caregiver time of 10.7 hours, translating to total societal cost savings of $2,502.

However, the long-term impacts of slowing disease progression on quantifiable measures assessing changes in functional abilities and behavioral symptoms of individuals with AD are less well-studied. The present study addresses this evidence gap using a standard empirical measure of disease progression, the CDR-SB, correlating hypothetical reductions in early AD (MCI and mild AD dementia) progression with projected changes in functional ability (using the Functional Activities Questionnaire; FAQ), behavioral symptoms (using the Neuropsychiatric Inventory Questionnaire; NPI-Q), and self-reliance or independent living, over a period of five years.

Methods

Data sources

The primary analysis was conducted using publicly available data from the prospectively collected US National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and the neuropathology (NP) dataset (which contains autopsy data for a subset of UDS participants) (19, 20). A sensitivity analysis was conducted with data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, with the goal of assessing the robustness of the findings of the primary analysis in the NACC sample and improving the study reproducibility and generalizability across different data sources.

The NACC implemented the UDS in 2005 and it is responsible for maintaining this cumulative database which includes data contributed by the 42 past and present Alzheimer's Disease Centers (ADCs) supported by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) (21, 22). Total enrolled participants in the UDS (N~45,000) reflects the total cumulative enrollment at the ADCs since 2005, representing a range of cognitive status — normal cognition, MCI, and dementia. The UDS also includes information gathered using standardized protocols on sociodemographic characteristics, medical and family history (including apolipoprotein E [APOE] ε4 genotype), as well as clinical information on motor, functional, and neuropsychiatric status. The UDS provides longitudinal

data, and the standard protocol requires approximately annual follow-up by trained clinicians for as long as individuals are able to participate. Thus, the typical time window between consecutive visits is approximately 12 months. The NP dataset provides carefully curated post-mortem information on neuropathological features associated with cognitive impairment in neurodegenerative disease including Alzheimer's disease (23). In addition to age and date of death, the NP dataset includes information regarding the presence of neuropathological features for most major dementias.

Study design and sample selection

This retrospective observational study used data from NACC, prospectively collected between the period from June 2005 to November 2021. The selected sample included participants with confirmed early symptomatic AD, encompassing both MCI and mild AD dementia, identified by requiring at least one visit with a CDR-SB score of 0.5-9.0 points (inclusive), a primary AD etiology for at least 50% of visits (including the most recent visit), and one AD etiology (primary or contributing) on or after the index date. The index date was defined as the first occurrence of both a clinician diagnosis of MCI or dementia and a CDR-SB score of 0.5-9.0 (inclusive), with no previous visit with CDR-SB >9.0. Participants were further required to have confirmed positive amyloid pathology, defined as either (1) abnormally elevated amyloid on a positron emission tomography scan, or (2) abnormally low amyloid in cerebrospinal fluid ante-mortem, or (3) autopsy result consistent with frequent density of neocortical neuritic plaques or Braak stage V or VI for neurofibrillary degeneration (24), and to have complete information on demographic characteristics and outcomes (described in the Study measures section below) at index date. The maximum follow-up was five years, reflecting the available sample of respondents with at least two visits after index date required with complete outcome information that allows for robust analysis of study outcomes.

Study measures

Participant characteristics evaluated on the index date included age, sex, race/ethnicity, APOE ε4 genotype status, comorbidities such as hypertension, depression, and diabetes, and AD-related medications such as memantine and donepezil. AD-related clinical outcomes (cognitive, functional, behavioral) evaluated at index and subsequent visits included CDR-SB as an overall measure of disease progression reflecting the core symptoms and impacts of AD, consisting of six domains assessing cognition and function (memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care), with a range of 0 to 18 (higher scores indicating greater impairment) (25-27); FAQ, which measures the ability to perform activities of daily living in 10 areas of functioning (financial skills, time and orientation, communication, travel and transportation, shopping, household chores, meal preparation, medication management, hobbies and interests, and personal care), with a range from 0 to 30 and with higher values indicating worse function and a score less than nine indicating normal function (28); NPI-Q, which measures the presence, severity, and associated impact of 12 symptoms (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbances, nighttime behaviors, and appetite and eating problems), with a range of 0 to 36 (higher values indicating worse neuropsychiatric symptoms) (29); self-reliance and ability to live independently, which was reported by the participants in the database on four levels, i.e., able to live independently (level 1), requires some assistance with complex activities (level 2), requires some assistance with basic activities (level 3), and is completely dependent, i.e. is unable to perform basic activities of daily living (level 4) and was recoded as a binary outcome, defined as being completely dependent (level 4) vs. not (levels 1-3) at any given visit. The decision to assess the implications of slowing disease progression on likelihood of complete dependence was informed by its profound clinical significance and public health implications. This level of dependence has significant consequences for both patients and caregivers, as it often indicates advanced disease progression and a higher burden of care.

Statistical analysis

Participant characteristics and clinical outcomes were assessed on the index date for the overall sample and stratified by MCI and dementia diagnosis, as of the index date. The effects of hypothetical reductions in disease progression on functional and neuropsychiatric outcomes were estimated, separately for participants with a diagnosis of MCI or dementia at index date, following a three-step procedure. First, mixed models for repeated measures (MMRM) were used to estimate least-square (LS) mean changes in empirical CDR-SB scores from index visit through year five. Following this, associations between LS mean change in CDR-SB from index to year five visit (estimated using MMRM) and key outcomes were assessed among participants with complete data on the covariates adjusted for in the models (described below). Specifically, linear regression was used to model continuous outcomes for FAQ and NPI-Q, whereas logistic regression was used to model level of dependence as a binary outcome, either completely dependent or else not completely dependent at year five. The results from the logistic regression models were then translated into average marginal effects (AMEs) based on predicted probabilities of complete

dependence, to express estimates in terms of probabilities rather than odds ratios. Predicted probabilities were calculated given relevant values in the key independent variable (i.e., change from baseline in CDR-SB), while holding constant the values of the covariates included in the model, and contrasts between the predicted probabilities in the different scenarios were averaged across all respondents in the dataset. All models adjusted for age, sex, APOE ε4 genotype, hypercholesterolemia, hypertension, depression, and cognitive and functional characteristics (i.e., CDR-SB, FAQ, NPI-Q, dependence) at index date. Only respondents with full information were used in the models; no imputation of missing data was conducted. Finally, the projected impact of hypothetical reductions in LS mean change in CDR-SB on outcomes was quantified by contrasting the change in scores from index (for FAQ and NPI-Q) to year five, and the percentage of participants with complete dependence at year five, respectively, under natural disease progression compared with slowing disease progression by 20% or 30%. All analyses were conducted using SAS Enterprise Guide version 7.15 and R version 3.6.2.

Sensitivity analysis

The sensitivity analysis was conducted in ADNI, a prospective, longitudinal multi-center (63 centers in the US and Canada) cohort study of participants (aged 55-90 years) initiated in 2004 and tasked with investigating the use of clinical, imaging, genetic, and biochemical biomarkers for early detection and tracking of AD (30). The ADNI study was approved by local Institutional Review Boards (IRB) at each site and written informed consent was obtained from all participants.

The study sample included early AD participants that had at least one clinical center visit with a clinical assessment of MCI, early MCI, late MCI, AD or dementia and had brain Aβ-positive status, defined as cerebrospinal fluid Aβ <192 pg/ml or florobetapir positron emission tomography (PET) global cortical uptake >1.11 standardized uptake value ratio (SUVR) or florobetaben PET global cortical uptake >1.08 SUVR. The index date in ADNI was defined as the date of the first visit with a clinical diagnosis of MCI or dementia. Subsequent visits were approximately 9-15 months apart, and participants were followed until the earliest of either death or last visit available (up to four years). Finally, participants were required to have complete demographic (age, sex, visit year, ethnicity, race, education, and marital status) and outcome information (CDR-SB, FAQ, and MMSE) at the index visit, and at least two visits after the index date with complete outcome information (Supplemental Figure A1).

At the index visit, participants' demographic information (i.e., age, gender, race, ethnicity, education, marital status), disease characteristics (i.e., APOE ε4 genotype status), and cognitive (CDR-SB, MMSE, Alzheimer's Disease Assessment Scale Cognitive Subscales 11 [ADAS-Cog 11] and 13 [ADAS-Cog 13]) and functional (FAQ) characteristics were evaluated.

The effects of hypothetical slowing down of disease progression – as measured by changes in CDR-SB – were assessed using methods similar to those described in the main analysis (Statistical analysis section). However, due to smaller sample size and limited outcome availability, several modifications were made to the study sample and outcomes considered for this analysis. Specifically, MMRM were first used to estimate LS mean changes in CDR-SB from index over follow-up visits up to year 4. Then, linear regression was used to assess the association between LS mean change in CDR-SB score from index to year 4 and FAQ score (adjusting for age, sex, APOE ε4 genotype status, and FAQ score at index) in the participant subgroup with MCI at index date only. This was not possible in the dementia subgroup, due to an insufficient number of participants with 4-year data. Finally, the projected impacts of hypothetical slowing of disease progression on FAQ score were based on the coefficient of change in CDR-SB from the linear regression model and the LS mean change in CDR-SB in two different scenarios of slowing disease progression: 20% and 30% lesser change in CDR-SB. Under these different scenarios, the changes in FAQ score from index were compared to the change in FAQ under natural disease progression. The sensitivity analysis was only possible for the FAQ score in the ADNI cohort, due to the absence of NPI-Q and recording of level of dependence in the ADNI database.

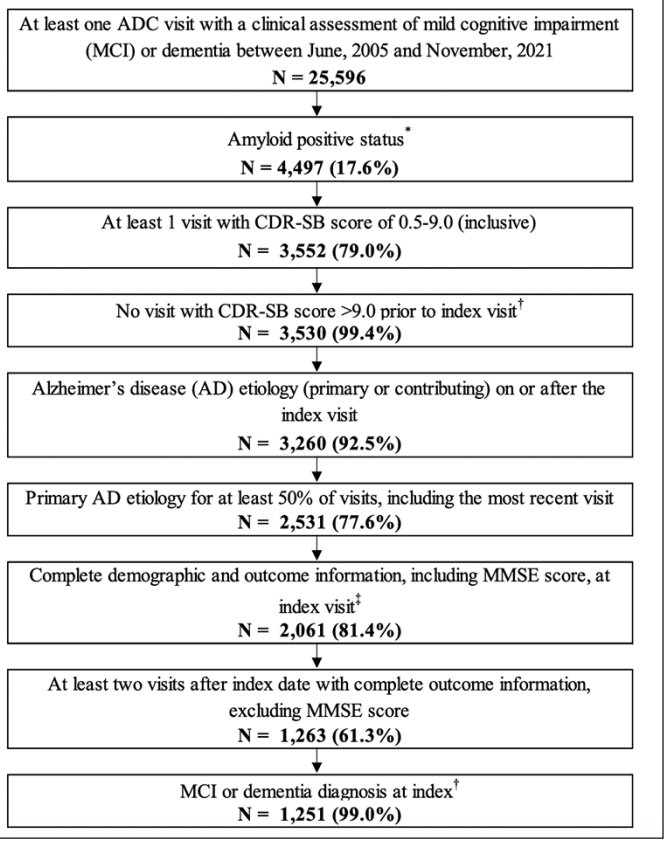
Results

Study population and characteristics

A total of 25,596 participants with at least one ADC visit and a clinical assessment of MCI or dementia between June 2005 and November 2021 were identified from the NACC UDS database, and of these, 1,251 participants met all inclusion criteria for further analysis (Figure 1). Participant characteristics assessed at index visit for the overall cohort with early symptomatic AD and for those classified as MCI (N=320; 25.6%) or mild dementia (N=931; 74.4%) at index are summarized in Table 1. Among all participants, the mean age (± standard deviation, SD) at index was 72.7 ± 9.7 years, 55.3% were male and 95.9% were White. The most common comorbidity at index was hypercholesterolemia (54.6%) and almost half of all participants (48.4%) had hypertension, with no significant differences in prevalence between the MCI and mild dementia subgroups. Differences were observed between the cohorts at index for prevalence of: psychiatric disorders (overall 49.2%), occurring in 42.8% of participants with MCI and 51.5% with mild dementia; depression (overall 43.2%) in 36.6% of participants with MCI and 45.4% with mild dementia; diabetes (overall 7.7%) in 12.2% of

participants with MCI and 6.1% with mild dementia. More participants overall had at least one copy of APOE ε4 (62.6%) compared with non-carriers (31.8%), 5.6% had unknown status, and there were no significant differences in prevalence between MCI and mild dementia subgroups. AD medication use at index date between the two subgroups differed, with memantine used by 9.1% and 38.0% of participants with MCI and mild dementia, respectively, while donepezil was used by 34.4% and 56.0%, respectively.

Figure 1. Flowchart of sample selection procedure



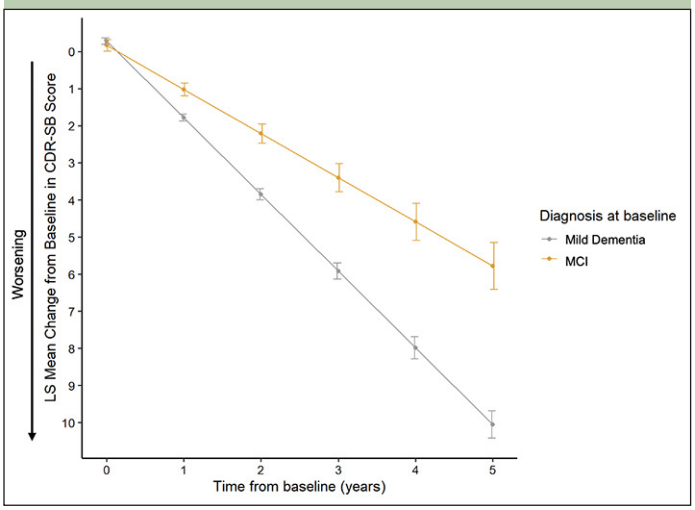
Abbreviations: ADC = Alzheimer's Disease Center, CDR-SB = Clinical Dementia Rating Sum of Boxes, MMSE = Mini-Mental State Examination, NACC = National Alzheimer's Coordinating Center, NPI-Q = Neuropsychiatric Inventory Questionnaire, FAQ = Functional Activities Questionnaire. Notes: *Amyloid positive status was defined as either abnormally elevated amyloid on positron emission tomography scan, abnormally low amyloid in cerebrospinal fluid (CSF), frequent density of neocortical neuritic plaques, or Braak stage for neurofibrillary degeneration of Stage V or Stage VI. †The index visit was defined as the first visit with CDR-SB score of 0.5-9.0 (inclusive). ‡Outcomes of interest included the CDR global score, CDR-SB, NPI-Q, FAQ, and level of dependence.

Overall mean (± SD) CDR-SB score at index was 3.9 ± 2.1, with mean scores of 1.7 ± 1.1 and 4.7 ± 1.9 for participants with MCI and mild dementia, respectively.

Impacts of potential slowing of disease progression on functional, behavioral, and dependence outcomes

Estimated LS mean changes in CDR-SB scores over five years were 5.78-point increase (95% CI: [5.15, 6.41]) for the MCI subgroup, and 10.05-point increase (95% CI: [9.68, 10.42]) for the mild dementia subgroup (Figure 2 and Supplemental Table A5).

Figure 2. Least-square mean change in CDR-SB from index visit to year 5 stratified by AD diagnosis at index visit



Abbreviations: AD: Alzheimer's Disease; CDR-SB: Clinical Dementia Rating- Sum of boxes; LS: Least squares; MCI: Mild Cognitive Impairment; MMRM: Mixed model for repeated measures. Notes: *Error bars indicate 95% confidence intervals for the MMRM LS means. Numerical details in Supplemental Table A5.

Increases in CDR-SB over time were significantly associated with increases in FAQ, NPI-Q, and level of dependence in both MCI and mild AD dementia subgroup. For participants with MCI, a one-unit increase in CDR-SB score from index to year five was associated with a 1.45-unit increase in FAQ score (95% CI: [1.18, 1.72], $P < 0.05$), a 0.44-unit increase in NPI-Q score (95% CI: [0.25, 0.63], $P < 0.05$), and a 53% increase in the odds of complete dependence (odds ratio [OR]: 1.53, 95% CI: [1.30, 1.89], $P < 0.05$), implying an average marginal increase of 0.04 in probability of complete dependence (Supplemental Tables A1-A4). For participants diagnosed with dementia at the index date, a one-unit increase in CDR-SB score from index to year five was associated with a 0.80-unit increase in FAQ score (95% CI: [0.66, 0.94], $P < 0.05$), 0.24-unit increase in NPI-Q score (95% CI: [0.09, 0.39], $P < 0.05$), and 55% increase in the odds of complete dependence (OR: 1.55, 95% CI: [1.41, 1.72], $P < 0.05$), equivalent to an average increase of 0.07 in probability of complete dependence given the observed rate of disease progression and temporal associations between the study outcomes over 5 years (Supplemental Tables A1-A4).

The impact of slowing disease progression by 20% and 30% in comparison with the normal course of progression over five years on functional and behavioral outcomes is shown in Figure 3. For example, in response to slowing disease progression by 20% over five years relative to natural progression (i.e., 0% slowing), the model projects a lesser FAQ score increase by 1.7 points (10.8% difference) for MCI participants and 1.6 points (12.9% difference) for those with mild dementia (Figure

Table 1. Characteristics of participants included in the study sample at index date

	Overall N = 1,251	MCI N = 320 (25.6%)	Mild Dementia N = 931 (74.4%)	p-value
Socio-demographic characteristics				
Age at index (years)	72.7 ± 9.7	73.6 ± 8.8	72.4 ± 10.0	< 0.05 *
Male	55.3%	57.2%	54.7%	0.474
Race				
White	95.9%	96.3%	95.8%	0.858
Black or African American	2.5%	2.5%	2.5%	1.000
Other	1.6%	1.3%	1.7%	0.796
Hispanic ethnicity	3.8%	4.1%	3.8%	0.940
Additional characteristics and medical history				
APOE ε4 genotype status				
Non-carrier	31.8%	30.0%	32.4%	0.460
Carrier	62.6%	63.4%	62.3%	0.767
Unknown	5.6%	6.6%	5.3%	0.465
Select comorbidities				
Hypercholesterolemia	54.6%	56.9%	53.8%	0.377
Hypertension	48.4%	47.8%	48.5%	0.871
Depression	43.2%	36.6%	45.4%	< 0.01 *
Diabetes	7.7%	12.2%	6.1%	< 0.001 *
Psychiatric disorder	49.2%	42.8%	51.5%	< 0.01 *
Cognitive and functional characteristics				
CDR-SB	3.9 ± 2.1	1.7 ± 1.1	4.7 ± 1.9	< 0.001 *
MMSE	23.2 ± 4.5	26.7 ± 2.5	22.0 ± 4.4	< 0.001 *
FAQ	11.3 ± 7.7	4.4 ± 4.7	13.6 ± 7.0	< 0.001 *
FAQ < 9	40.3%	85.3%	24.8%	< 0.001 *
Level of independence				< 0.001 *
Able to live independently	32.2%	63.8%	21.4%	
Requires some assistance with complex activities	53.6%	34.7%	60.0%	
Requires some assistance with basic activities	13.1%	1.6%	17.1%	
Completely dependent	1.1%	0.0%	1.5%	
Behavioral characteristics				
NPI-Q	3.7 ± 3.6	2.5 ± 2.8	4.2 ± 3.8	< 0.001 *
AD medications				
Memantine	30.6%	9.1%	38.0%	< 0.001 *
Donepezil	50.4%	34.4%	56.0%	< 0.001 *

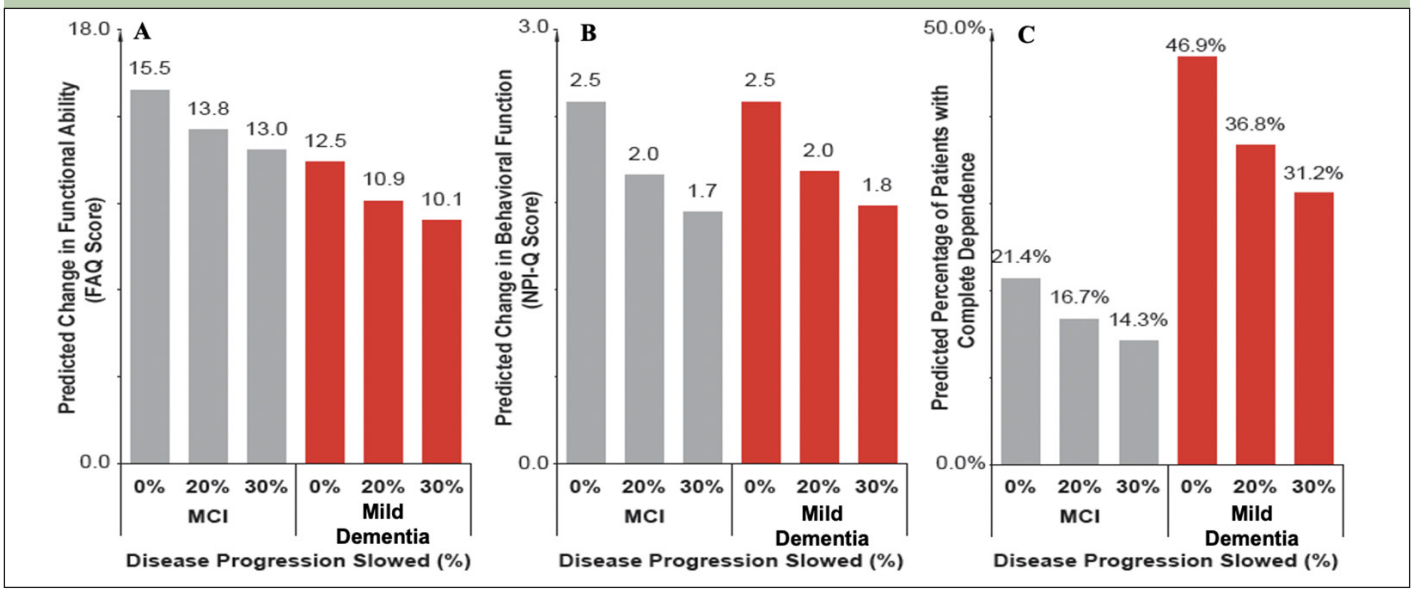
Abbreviations: AD: Alzheimer's disease; APOE ε4: apolipoprotein E for the ε4 allele; CDR-SB: Clinical Dementia Rating Sum of Boxes; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; FAQ: Functional Activities Questionnaire; NPI-Q: Neuropsychiatric Inventory Questionnaire. Notes: Some percentages do not add up to 100% due to rounding. Means and standard deviations are shown for continuous characteristics; percentages are shown for categorical characteristics. P-values were estimated from two-sample t-tests for continuous variables and chi-square tests for categorical variables. P-values are shown solely for information purposes, to display the baseline differences between the two subgroups. Outcomes were analyzed separately within each subgroup, and no statistical comparisons of outcomes were conducted between the subgroups.

3A). Similarly, a 20% reduction in disease progression was associated with a slower deterioration (score increase) in NPI-Q by 0.5 points (20.3% difference) for the MCI subgroup and 0.5 points (19.3% difference) for those with mild dementia, compared with natural progression (Figure 3B). Finally, a 20% reduction in disease progression assessed by CDR-SB projects that 16.7% of the MCI subgroup would be completely dependent at year 5 rather than 21.4% with a normal course of progression (4.7 percentage points or 22.2% difference), and 36.8% of the mild dementia subgroup would be completely dependent at year 5 rather than 46.9% with normal progression (10.1 percentage points or 21.6% difference) (Figure 3C). The expected benefits were larger with an estimated 30% slowdown in the disease progression.

Sensitivity analysis using the ADNI database

Of 1,488 participants from the ADNI data who were identified with clinically validated MCI or mild AD, 495 participants fulfilled eligibility criteria for inclusion in this analysis (Supplemental Figure A1). Among all 495

Figure 3. Impact of potential slowing of disease progression on functional (panel A), behavioral (panel B), and dependence (panel C) outcomes over 5 years



Abbreviations: APOE ε4: apolipoprotein E for the ε4 allele; CDR-SB: Clinical Dementia Rating - Sum of Boxes; GLM: generalized linear model; LS: least squares; MCI: mild cognitive impairment; MMRM: mixed model for repeated measures; NPI-Q: Neuropsychiatric Inventory Questionnaire. Notes: * Disease progression was represented by LS mean change in CDR-SB score (range 0-18, with higher values indicating worse cognition and/or function), and estimated using a linear MMRM as 5.8 among MCI participants and 10.0 among dementia participants at year 5. †Functional progression was represented by change in FAQ score (range 0-30, with higher values indicating worse function). ‡Behavioral progression was represented by changes in NPI-Q (range 0-36), with higher values indicating worse neuropsychiatric symptoms. §Complete dependence was defined as a categorical outcome (i.e., 1 = completely dependent, 0 = able to live independently/requires some assistance). ||The relationships between change in FAQ/NPI-Q score and CDR-SB score from index to visit 5 were estimated using linear regression models. The relationship between level of dependence at year 5 and change in CDR-SB score from index to year 5 was estimated from the average marginal effects for a logistic regression model. All models adjusted for respective scores and patient characteristics at index. {Projected changes in FAQ and NPI-Q scores, respectively, under different scenarios of slowing down CDR-SB deterioration by a rate of r% (20% or 30%, respectively) were calculated as: $\Delta Score = \Delta CDR\text{-}SB \times \beta CDR\text{-}SB \times (100\text{-}r\%)/100$, where ΔScore is the mean change in FAQ or NPI-Q score, from index over 5 years, ΔCDR-SB is the LS mean change in CDR-SB at year 5, and βCDR-SB is the adjusted linear regression coefficient of CDR-SB. Projected percentages of participants with complete dependence at year 5 were calculated by estimating the predicted probabilities from the multivariate logistic regression model of complete dependence on CDR-SB at different values of CDR-SB mean change over 5 years under different scenarios of slowdown of disease progression.

participants, the mean (± SD) age at index was 73.5 ± 7.3 years, 59.0% were male, 95.2% were White, 64.9% had at least one copy of the APOE ε4 allele, 80.8% (N = 400) were diagnosed with MCI and 19.2% (N = 95) were diagnosed with mild dementia at the index date (Supplemental Table A6). Mean CDR-SB score was 2.0 ± 1.5, MMSE was 26.7 ± 2.5, FAQ was 5.1 ± 5.8, and 76% of participants had normal function FAQ (< 9).

Due to insufficient number of participants in the dementia subgroup, we report sensitivity analysis only for the MCI subgroup. LS mean increase in CDR-SB score in the MCI subgroup over four years from index date was 2.69 (SE: 0.17; 95% CI: [2.34, 3.03]) (Supplemental Figure A2 and Supplemental Table A8). A one-unit change in CDR-SB score from index to year four was associated with a 1.98-unit change in FAQ score (95% CI: 1.78, 2.18, $P < 0.05$), adjusting for select participants' characteristics at index visit: age, sex, APOE ε4 genotype status, and FAQ score (Supplemental Table A8). The model projects that delaying disease progression (i.e., reduced CDR-SB) by 20% or 30% at year 4 would preserve functional ability (as measured by FAQ) by 1.1 points (19.7%) and 1.6 points (29.6%), respectively, compared to natural disease progression (Supplemental Figure A3).

Discussion

This retrospective study of participants enrolled in the NACC UDS quantified how functional and behavioral outcomes in amyloid-positive individuals with early symptomatic AD may be projected to respond over a longer time horizon, based on a presumed slowing of disease progression as measured by changes in CDR-SB. The sample consisted of two subgroups of participants, those with MCI and those with mild dementia, based on their diagnosis at index visit.

Natural progression in the participants was observed empirically to increase steadily over time, but with different trajectories in the two subgroups based on disease severity at index, with CDR-SB score rising approximately 1 point on average every year in participants with MCI, and twice as fast in those with mild dementia. This finding is consistent with prior studies which found faster progression of individuals with dementia vs. those with MCI. For example, Samtani et al. (2014) found that their best-fitting longitudinal progression model estimated an annual progression rate of 0.5 points in ADNI participants with late MCI and 1.4 points in those with mild AD (31). Similarly, Williams et al. (2013) found an annual progression

rate of 1.43 points in an MCI cohort and 1.91 points in an early AD cohort using data from the Knight Alzheimer's Disease Research Center (Knight ADRC) study (32). Increases in CDR-SB scores indicating disease progression were associated quantitatively with declines in functional abilities (increase in FAQ), behavioral and neuropsychiatric symptoms (increase in NPI-Q), as well as ability to live independently. The quantitative effects of slowing disease progression by 20% or 30% on functional, behavioral and dependence outcomes were broadly similar between the two subgroups and across the outcomes. For example, reducing disease progression by 20% resulted in approximately 22% lower probability of complete dependence in both subgroups compared with natural progression. In the case of FAQ scores, the absolute changes observed during normal disease progression over five years in the MCI subgroup (15.5 units) were greater than those observed in the dementia subgroup (12.5). This may be attributable to the ceiling effect among participants with early symptomatic AD since those with mild dementia diagnosis at index had considerably higher FAQ score on average than those with MCI diagnosis (13.6 vs. 4.4). Moreover, the FAQ may be more sensitive to cognitive decline in the MCI sample due to its design as a measure of instrumental activities of daily living, which have previously demonstrated greater sensitivity in MCI compared to mild AD (33).

Despite these differences, reductions in disease progression had proportionately similar effects on changes in FAQ scores in the MCI and mild dementia subgroups – 10.8% vs 12.9% change with a 20% reduction in disease progression, respectively – implying that relative changes in functional capacity are affected similarly by disease progression in the two subgroups. Projected changes in behavioral symptoms measured using NPI-Q were also similar between the two subgroups, both in terms of proportional effects of reduced disease progression, and in absolute changes in NPI-Q scores, implying that relative changes in behavioral symptom severity due to disease progression are quantitatively similar between participants with MCI or mild dementia at index.

The effects on FAQ of hypothetical graded reductions in disease progression were qualitatively similar in a sensitivity analysis based on a different study population (ADNI) of participants diagnosed with MCI at index date, albeit with differences in absolute changes in FAQ. Incorporating ADNI data has the benefit of providing a broader context for our findings. ADNI is a well-established longitudinal study with extensive neuroimaging and clinical assessments, offering a unique perspective on cognitive decline in individuals with early AD. The inclusion of ADNI data allows for a comparison of results across multiple datasets, enhancing the generalizability of our findings and supporting the notion that the relationship between cognition and function is robust, albeit with some variability that could be attributed to cohort-specific factors. In the NACC cohort, we observed more substantial reductions in FAQ scores in response to slowing of disease progression, indicating a potentially greater sensitivity of this measure to cognitive decline in this population. Conversely, in the ADNI cohort, while the qualitative trends remained consistent, the magnitude of FAQ score increase was somewhat milder. This observation may be attributable to the differences in study protocols between the two datasets, particularly as they relate to baseline participant characteristics and frequencies of assessment.

To the best of our knowledge, this is the first study to estimate the long-term effects of potential slowing in AD progression among participants with amyloid-positive early symptomatic AD – a population expected to benefit from the emerging treatments for AD – on their functional and behavioral abilities. Nonetheless, the findings for the present study are consistent with the positive effects of slowing disease progression on economic and caregiver burden observed by others. For example, using a similar approach to estimate the effects of slowing disease progression as the present study, Lenox-Smith et al (2018) found that delaying disease progression by 30% (as measured by MMSE) was associated with savings of £670, largely attributable to reductions in caregiver hours (15). Other studies from different regions investigating cost savings attributed to delayed AD progression reached similar conclusions; analysis of data from GERAS-EU predicted that informal caregiver time at each level of AD dementia severity accounted for 54–65% of the 18-month total societal costs (16), and analysis of data from GERAS-US predicted that a 30% reduced AD progression over 36 months (measured by MMSE) translated to reduced caregiver time and total societal cost savings of $2,502 (compared to an increase of $8,084 per person with natural progression over the same time period) (18). These results are consistent with the present study indicating that the relatively large increases in dependence with no delay in disease progression could be mitigated substantially (approximately 33%) with a 30% reduction in disease progression. Taken together, these findings help quantify the potential value of slowing disease progression with emerging treatments among participants with confirmed amyloid pathology in the early stages of symptomatic AD from patient, caregiver, and health system perspectives. These findings help contextualize outcomes of clinical trials for treatments with disease modifying potential. However, additional research, for example, among participants treated with the recently approved treatments for AD, is needed to corroborate the findings from the present study in the real-world.

Limitations

This study was subject to certain limitations. Although the study utilized data from a diverse set of participants across multiple ADCs in the US, the results may not

be generalizable to the entire US population as NACC participants represent a clinic-based convenience sample and tend to be highly educated. Relatedly, almost 96% of the patients in the study sample were White, thus potentially limiting the generalizability of our study in a more racially diverse population. Additionally, individual ADCs recruit and enroll participants according to their own protocols and the varying inclusion/exclusion criteria may introduce bias into the sample. Relatedly, the confirmation of amyloid pathology included postmortem analysis in a subgroup of participants, therefore the study sample may not reflect the population encountered in real-world clinical practice. Overall, while requiring complete outcome information for multiple follow-up visits allows for the estimation of longitudinal changes in the variable of interest, it may also introduce selection bias and further diminish the generalizability of the results. Further, the proportion of participants with available data declined considerably over time. Although the precise reason for attrition is unavailable in the data, participants with worsening cognitive impairment, neuropsychiatric symptoms, and difficulty with functional activities may be more likely to be lost to follow-up (34). Consequently, the long-term deterioration in all outcomes, particularly in later years following the index date, may be underestimated. Additionally, although the models used to estimate effects of hypothetical reductions in disease progression adjusted for observable characteristics at index, the effects of unobserved heterogeneity are not known. Moreover, there are differences in the overall sample sizes between the two study cohorts, and within cohorts for subgroups with MCI and mild dementia. ADNI and NACCUDS represent distinct datasets with varying participant populations, recruitment strategies, and data collection protocols, leading to differences in the number of participants available for analysis. The differences in sample sizes both within and across cohorts can influence the stability and reliability of our results. Larger sample sizes generally provide more statistical power, enabling the detection of smaller effects or differences. Therefore, differences in sample size between groups or cohorts can affect the validity and generalizability of our findings. Finally, estimates of hypothetical impacts from slowing down disease progression should be interpreted with caution, as causal effects on the outcomes studied were not explicitly identified.

Conclusions

AD is a complex disease that affects multiple aspects of an individual's life, with increased impairment in daily tasks, worsening of behavioral symptoms, and increased reliance on others for regular care. Supporting this premise, the present study shows that delaying disease progression in individuals with early symptomatic amyloid-positive AD can have potential long-term benefits across several clinical domains. Specifically, a slowing of clinical disease progression (as measured by changes in CDR-SB) is estimated to have similar impacts across functional, behavioral, and autonomy outcomes, which indicates that the potential benefits of slowing the progression of AD can extend beyond an impact on cognition to other areas of an individual's life. Furthermore, our findings suggest that slowing disease progression would delay AD-related function and dependence similarly in individuals with MCI and mild dementia. Future empirical studies among individuals treated with approved therapies with disease modifying potential are needed to corroborate these findings in the real-world.

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Ethical standards: Because NACC UDS and NP data are completely de-identified, and compliant with patient privacy obligations under the Health Insurance Portability and Accountability Act, this study was not subject to Institutional Review Board approval and a formal Consent to Release Information form was therefore not required. All methods were performed in accordance with relevant guidelines and regulations, including the principles of the Declaration of Helsinki.

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