Received: 18 November 2024 | Revised: 25 February 2025 | Accepted: 27 February 2025

DOI: 10.1002/trc2.70074

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Combination therapy targeting Alzheimer's disease risk factors is associated with a significant delay in Alzheimer's disease–related cognitive decline

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

Yuan Shang and Georgina Torrandell-Haro are co-first authors.

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Funding information
National Institute on Aging, Grant/Award Numbers: 5R01AG057931-02, P01AG026572; Alzheimer's Drug Discovery Foundation

Abstract

BACKGROUND: Alzheimer's disease (AD) cognitive decline can be a major contributor to loss of independent living. Therapeutic strategies that alter the course of cognitive deterioration have the potential to sustain activities of daily living, promote quality of life, and delay transition to nursing-home care.

METHODS: We performed longitudinal linear regression analysis of National Alzheimer's Coordinating Center (NACC) cognitive data from 7653 mild dementia AD participants at baseline with at least one medication for diabetes (DBMD), lipid-lowering (LIPL), anti-hypertensive (AHTN), and non-steroidal anti-inflammatory (NSD) medications or any combination in 5684 (74%) participants and in 1969 (26%) participants with no study-relevant prescriptions over 10 years. Change in cognitive function was determined by Mini-Mental State Examination (MMSE) and *CDR® Dementia Staging Instrument* Sum of Boxes (CDR-SB) scores relative to non-treated participants stratified by sex and apolipoprotein E (*APOE*) genotype. Validation analysis was performed using Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

RESULTS: Combination of DBMD+LIPL+AHTN+NSD (QuadRx) resulted in a significant 46% MMSE and 32% CDR-SB delay in cognitive decline at 5 years, which was sustained at 10 years with a delay in decline of 47% MMSE and 33% CDR-SB. QuadRx was equally effective for the delay of cognitive decline in both females and males at 5 and 10 years. QuadRx mitigated the impact of the *APOE* ε4 genotype. Findings were validated in ADNI AD participants in which QuadRx was associated with a significant 60% MMSE delay in cognitive decline at 1 and 2 years.

CONCLUSIONS: Combination therapy was associated with a significant delay in cognitive decline in NACC AD participants at a magnitude comparable to or greater than amyloid beta immunomodulators. Further, the delay in decline was sustained for 10 years. The impact of QuadRx to delay cognitive decline was validated in deeply characterized ADNI participants. These data support combination therapy in persons with AD risk factors to alter the course of AD that persists for a decade, enabling cognitive function at a magnitude associated with independent living.

KEYWORDS
Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative, Alzheimer's disease risk factors, combination therapy, National Alzheimer's Coordinating Center

Highlights

- QuadRx slowed Alzheimer's disease (AD) cognitive decline by 47% in the National Alzheimer's Coordinating Center NACC and 60% in Alzheimer's Disease Neuroimaging Initiative ADNI participants.
- Combination therapy exhibited additive and synergistic slowing of cognitive decline.
- QuadRx was equally effective in females and males at 5 and 10 years.
- QuadRx mitigated the impact of the apolipoprotein E ε4 genotype.
- QuadRx was effective in AD participants reporting drug use for their AD risk factor.

1 | BACKGROUND

Alzheimer's disease (AD) is a multifactorial and complex disease associated with multiple risk factors including diabetes,[1] hyperlipidemia,[2] hypertension,[3] and inflammation[4] and influenced by sex and apolipoprotein E (*APOE*) genotype.[5,6] US Food and Drug Administration (FDA)-approved immunotherapies targeting amyloid show promise in slowing cognitive decline during mild AD.[7–9] Monoclonal antibodies slow the rate of decline but do not reverse the disease course and include a risk of amyloid-related imaging abnormalities (ARIA)/ARIA-edema and economic burden.[10]

The preclinical phase of AD spans 20 years prior to diagnosis.[11] Multiple risk factor conditions can contribute to preclinical AD and ultimately initiate disease if not effectively controlled.[12] Based on our targeted-risk AD prevention (TRAP) strategy, 364 AD risk factors were identified with diabetes, dyslipidemia, hypertension, and inflammation as main drivers of AD risk.[13] These AD risk factors were associated with 629 FDA-approved drugs, 46 of which were identified as high-confidence therapies to reduce the risk of AD.[13] Top-ranked therapeutics included glucose regulating, lipid lowering, antihypertensive, and anti-inflammatory therapeutics.[13] Pathway analysis of biological signatures of these drug classes revealed that a combinatorial approach for AD could exert greater efficacy compared to a single-target approach.[13] Impact of drugs targeting diabetes, dyslipidemia, hypertension, and inflammation and their impact on reducing the risk of AD is well described.[14–21] In contrast, outcomes of clinical trials of these therapeutics in AD patients who did not have the clinical condition for which the drug was developed were not effective in altering the course of AD.[22–35] However, a subset of responders to these therapeutics was identified within unsuccessful clinical trials, which highlighted the impact of sex and *APOE* genotype in treatment outcomes.[36–38] Responder analyses of these trials identified *APOE* ε4 carriers as responders to lipid-lowering (LIPL) therapy statins[36] and male *APOE* ε4 non-carriers as responders to diabetes medication.[37,38]

We investigated the rate of progression of cognitive decline in real-world clinical data within the National Alzheimer's Coordinating Center (NACC) dataset. Our analyses aimed to assess the impact of therapeutics for AD risk factors, specifically: (1) diabetes (DBMD), (2) LIPL, (3) antihypertensive (AHTN), and (4) non-steroidal anti-inflammatory (NSD) medications, alone and in combination, in AD participants reporting history of these AD risk factors, each of which is specifically targeted by these medications.

2 | METHODS

2.1 | Data source

This study was conducted using the NACC database. The NACC database includes longitudinal data from 48,605 participants enrolled in 33 different Alzheimer's Disease Research Centers (ADRCs). This analysis used the Uniform Data Set (UDS) within the NACC database, which contains subject demographics, diagnosis, prescription records, and neurological examination findings from 2005 to the present (v62, last access September 2023). NACC UDS version 3.0 was used with all visits for all participants as of June 2023 data freeze.

NACC findings were validated using ADNIMERGE in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, 2004 to 2022 longitudinal data (last access May 2024).[39]

2.2 | Study design and variables

NACC participants with a minimum of two visits, an AD diagnosis (D1 form), and demographics (A1 form) were selected as the initial cohort (Table S1 in supporting information). Medication use was self-reported. Therapeutics in the following categories were included for analyses: DBMD, LIPL, NSD, and AHTN medications (Table S1, S2 in supporting information). Participants were categorized into therapeutic groups based on whether they received mono-, di-, tri-, or quadruplet treatment of selected study drugs. Each participant was assigned to only one therapeutic group. The control group (NONE) was defined as AD participants who did not report the use of any medication and did not report a history of diabetes, hypercholesterolemia, or hypertension. To evaluate the potential impact driven by AD risk conditions on cognitive function, the group of AD participants reporting at least one medical condition but who did not report any medication use (NONE with conditions) were analyzed separately (Table S3 in supporting information).

Validation analysis was conducted using ADNI data from 411 AD participants. Prescription records were assigned to the categories DBMD, LIPL, AHTN, and NSD. The control group was defined as participants without prescription records for DBMD, LIPL, AHTN, or NSD (NONE). Treatment groups were divided into participants (1) with prescription records for the quadruplet DBMD+LIPL+AHTN+NSD (QuadRx) or (2) with at least one prescription record for DBMD, LIPL, AHTN, or NSD, or pair, or triplet combinations.

2.3 | Cognitive outcomes

Outcomes were change in two cognitive tests used in both clinical trials and clinical care:[7,8,40] Mini-Mental State Examination (MMSE)[41] and *CDR® Dementia Staging Instrument* Sum of Boxes (CDR-SB)[42] scores (Method S1 in supporting information).

MMSE and CDR-SB were collected by trained clinicians (C1 and B4 NACC forms; Table S1). MMSE and CDR-SB performance were evaluated at 2-, 5-, and 10-year assessments compared to baseline in NACC and at 1 and 2 years in ADNI. MMSE and CDR-SB change from baseline for each therapeutic group was assessed based on sex and *APOE* genotype.

2.4 | Statistical analysis

Statistical analyses were conducted using R (v4.2.1). Descriptive statistics were generated to characterize the study cohort at their first visits (baseline) when diagnosed with AD using all study variables. Continuous variables among groups were compared using one-way analysis of variance. A chi-square test was used to compare categorical variables.

Linear regression, incorporating random slopes and intercepts, was used to model progression of cognitive performance by time and medications.[43] All analyses of CDR-SB and MMSE trajectories were adjusted for age at recruitment and baseline scores to adjust for potential confounders. Secondary analyses adjusting for level of education in addition to age and baseline scores were performed. Changes in cognition were predicted with 95% confidence intervals. Percent delay in cognitive decline for treated groups was calculated relative to control (NONE).

Regression plots were created using ggplot2[44,] and slopes were compared using emmeans.[43] Regression coefficients between treated and non-treated groups were reported; *P* values were adjusted using Dunnett test for multiple comparisons.

The impact of history of stroke, transient ischemic attack (TIA), antipsychotic drug use, and participant mortality between follow-up visits (Tables S1, S2) was evaluated by performing secondary analyses excluding participants reporting a history of stroke and TIA, history of antipsychotic drug use, or participants who died between follow-up visits.

The impacts of sex and *APOE* genotype on treatment outcomes were evaluated using linear mixed-effects models with random

RESEARCH IN CONTEXT

1. **Systematic review**: Therapeutics targeting diabetes, dyslipidemia, hypertension, and inflammation significantly reduce the risk of Alzheimer's disease (AD). However, in these at-risk populations, there are non-responders that progress to AD. We sought to determine the impact of combination therapy targeting AD risk factors on the rate of cognitive decline in real-world AD patients within the National Alzheimer's Coordinating Center (NACC) dataset with validation using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.
2. **Interpretation**: Differences in cognitive decline profiles for each therapeutic and combinations thereof indicated significant slowing of cognitive decline that was effective in both sexes and across apolipoprotein E genotype. Evidence provided herein indicates that the QuadRx combination prescribed for AD risk factors significantly slowed cognitive decline in both NACC and ADNI AD participants at a magnitude comparable to or greater than amyloid beta immunomodulator interventions.
3. **Future directions**: These outcomes provide a therapeutic class framework for identification of specific drugs with greatest efficacy within each class that could be determined for optimized precision combination therapies using larger and comprehensive datasets.

slopes and intercepts by incorporating variables sex:medication or *APOE*:medication status. Pairwise comparisons between slopes were calculated and *P* values were adjusted using the Tukey test.

3 | RESULTS

3.1 | NACC and ADNI participants

The NACC database included 20,946 AD participants, of which 7653 had at least two visits and medication history for study-relevant therapeutics (Table S3, overall). The NACC cohort was balanced for sex (50% females), predominately White (85%), and non-Hispanic (92%). Of NACC AD participants, 47% were *APOE* ε4 carriers. At baseline, average MMSE and CDR-SB scores were 21.7 and 5.43, respectively, which corresponds to mild dementia diagnosis[42] (Table S3). Differences in demographics and baseline cognitive scores between treated and non-treated participants are reported in Table S4 in supporting information. Of all NACC participants, 5458 (71%) were prescribed at least one medication including DBMD, LIPL, AHTN, NSD, or any double or triple combination; 226 (3%) were prescribed the combination of DBMD+LIPL+AHTN+NSD (QuadRx); and 1969 (26%) had no prescription records for study-relevant medications (Figure S1a in supporting information). A subset of 887 participants within the untreated group (NONE with conditions) had a diagnosis of diabetes, hypercholesterolemia, or hypertension but did not report the use of either DBMD, LIPL, AHTN, or NSD (Figure S1b). DBMD alone (0.4%), DBMD+LIPL (0.6%), DBMD+NSD (0.3%), and DBMD+LIPL+NSD (0.4%) were prescribed to < 50 participants ($n < 50$) and therefore excluded from analysis (Figure S1, Table S3).

ADNI database included 2432 participants, of which 411 had a diagnosis of AD at baseline. Of those, 345 participants (84%) had at least one prescription record for DBMD, LIPL, AHTN, or NSD and 22 (5%) were prescribed QuadRx (Table S5 in supporting information) while 44 (11%) participants did not report medication use (control). Of ADNI AD participants, 43.8% were female and 65.7% were *APOE* ε4 carriers. The majority of participants were White (91.2%) and non-Hispanic (95.6%). Baseline cognitive scores were not significantly different between therapeutic groups with an average (standard deviation) baseline MMSE of 23.1 (2.19) and CDR-SB of 4.43 (1.69; Table S5).

3.2 | Association between therapies prescribed for AD risk factors and cognitive decline in NACC participants

Analyses of MMSE and CDR-SB scores in NACC participants indicated different trajectories of cognitive decline in AD participants at both 5 and 10 years (Figures 1, 2; and Figure S2 and Table S6 in supporting information).

Untreated AD participants (NONE control) experienced an MMSE decline of −9.3 (95% confidence interval [CI], [−9.7, −8.9]) at 5 years and −18.0 [−18.7, −17.2] at 10 years (Figure 1A,B) and CDR-SB decline of 6.3 [6.1, 6.6] at 5 years and 12.2 [11.7, 12.7] at 10 years (Figure 1C,D, Table S6). Participants with a diagnosis of an AD risk factor who did not report the use of study-relevant drugs (NONE with conditions) were not significantly different ($P = 0.99$) from AD controls (Figure S2). Untreated participants without these conditions (NONE control) or who remained untreated for them (NONE with conditions) experienced accelerated decline compared to those who received treatment (Figure 2, Figure S2).

Ranking of combination therapies based on cognitive decline is presented in Figure 2 and Table S6. An incremental treatment-dependent effect was evident: treating one risk factor slowed decline, treating two or three risk factors slowed decline further, and treating four AD risk factors (QuadRx) resulted in the greatest slowing of cognitive decline (Figure 2, Figure S2, Table S6).

QuadRx was associated with a significant 46% slowing of cognitive decline at 5 years and 47% at 10 years compared to untreated controls (NONE) as assessed by MMSE (−5.1 [−5.6, −4.6] at 5 years; −9.5 [−10.5, −8.4] at 10 years; $P < 0.001$; Figures 1A,B and 2A,B) and 32% and 33% as assessed by CDR-SB (4.3 [4.0, 4.6] at 5 years; 8.1 [7.5, 8.8] at 10 years; $P < 0.001$; Figures 1C,D and 2E,F). Over 10 years, the QuadRx exhibited a 1.7-fold decline in MMSE compared to the 7.7-fold decline of untreated controls (Figure 1B, $P < 0.001$). Over the same timeframe, cognitive decline in CDR-SB within the untreated group was 3.1-fold from baseline, whereas participants within the QuadRx group exhibited a 2.7-fold decline from baseline (Figure 1D, $P < 0.001$).

All analyses of CDR-SB and MMSE trajectories were adjusted for age at recruitment and baseline scores. Supplementary analyses, including level of education as a covariate, yielded results consistent with the primary findings (Figure S3 in supporting information). Additionally, the exclusion of participants with a history of stroke, TIA, and use of anti-psychotic agents, and who died between follow-up visits resulted in comparable outcomes (Figure S4 in supporting information). Moreover, the number of participants treated with FDA-approved medications for AD symptoms (Table S1, S2) did not significantly differ between QuadRx and NONE groups (chi-square test, $P = 0.53$), indicating that the use of FDA-approved AD medications did not impact the outcomes of these analyses.

3.3 | Association between therapies prescribed for AD risk factors and cognitive decline in ADNI participants

Validation analyses of cognitive decline were conducted in three groups of ADNI AD participants: (1) prescribed QuadRx therapy, (2) prescribed with one to three prescriptions of medications, and (3) not reporting use of study-relevant medications (NONE; Figures 1E–J and 2C,D,G,H and Table S7 in supporting information).

Consistent with NACC results, ADNI AD participants prescribed QuadRx exhibited a significant 60% delay in cognitive decline compared to untreated control (NONE) at 1 and 2 years assessed by MMSE (score change: −1.5 [−2.2, −0.7] at 1 year; −2.9 [−4.4, −1.5] at 2 years;

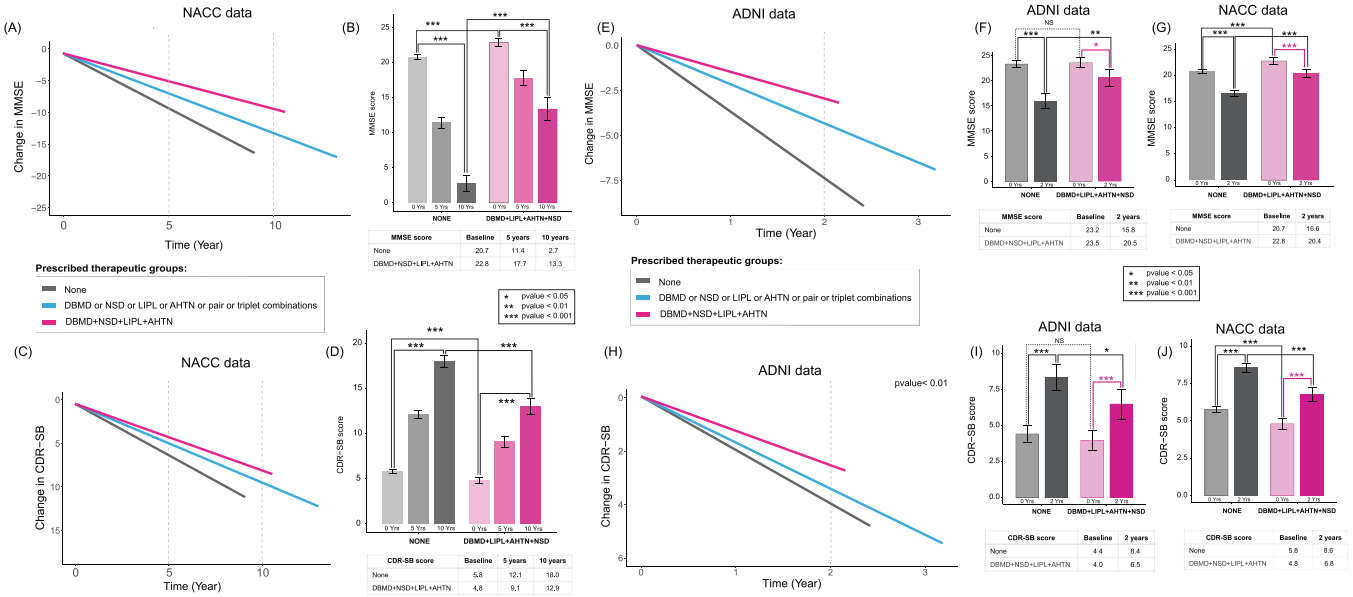

FIGURE 1 MMSE and CDR-SB in NACC and ADNI dataset. A, NACC MMSE score change from baseline over a 10-year period by therapeutic group (no treatment, treated with single, pair or triplet combinations). B, NACC MMSE scores at baseline, 5 years, and 10 years for Controls (None) and QuadRx (DBMD+NSD+LIPL+AHTN). C, NACC CDR-SB score change from baseline over a 10-year period by therapeutic group (no treatment, treated with single, pair, or triplet combinations). D, NACC CDR-SB score at baseline, 5 years, and 10 years for Controls (None) and QuadRx. E, ADNI MMSE score change from baseline over a 3-year period by therapeutic group (no treatment, treated with single, pair, or triplet combinations). F and G, MMSE score at baseline and 2 years for Controls (None) and QuadRx in ADNI and NACC, respectively. H, ADNI CDR-SB score change from baseline over a 3-year period by therapeutic group (no treatment, treated with single, pair, or triplet combinations). I and J, CDR-SB score at baseline and 2 years for Controls (None) and QuadRx in ADNI and NACC, respectively. ADNI, Alzheimer's Disease Neuroimaging Initiative; AHTN, antihypertensive drug; CDR-SB, *CDR® Dementia Staging Instrument* Sum of Boxes; DBMD, diabetes medication; LIPL, lipid lowering; NSD, non-steroidal anti-inflammatories; MMSE, Mini-Mental State Examination; NS, not significant; NACC, National Alzheimer's Coordinating Center; Yrs, years, 0 Yrs, baseline.

$P < 0.001$; Figures 1E,F and 2C,D, Table S7) and 37% and 36% at 1 and 2 years, respectively, assessed by CDR-SB (score change: 1.2 [0.8, 1.6] at 1 year; 2.5 [1.7, 3.3] at 2 years; $P = 0.04$; Figures 1H,I and 2G,H, Table S7).

Because ADNI data were limited to 2 years of drug exposure, we conducted an analysis of NACC cognitive outcomes at 2 years. Results of those analyses indicated that QuadRx was associated with a 41% (MMSE) and a 29% CDR-SB delay in cognitive decline at 2 years (Figure 1G–J).

3.4 | Sex differences

A significant sex difference was apparent in the rate of progression of cognitive decline as measured by CDR-SB in untreated NACC AD participants ($P = 0.02$) with females associated with more rapid cognitive decline compared to males (Figure 3A, dashed lines). QuadRx was associated with a significant delay in cognitive decline at 5 and 10 years that was equal for both females and males (Figure 3B,C).

In contrast, monotherapies exhibited significant sex-dependent delay in cognitive decline. Males treated with LIPL ($P < 0.001$) (Figure S5a in supporting information) or NSD only ($P < 0.01$; Figure S5f) exhibited greater slowing of cognitive decline (Table 1). Conversely, AHTN alone did not exhibit a sex-dependent association with cognition ($P = 0.92$; Figure S5d). However, when AHTN was combined with NSD, the combination resulted in males exhibiting a slower decline ($P = 0.01$) compared to females (Figure S5e). Females treated with LIPL alone (Figure S5a) were not significantly different from non-treated participants ($P = 0.54$), whereas LIPL combined with either AHTN or NSD resulted in a significant delay in cognitive decline ($P < 0.001$; Table 1).

The triplet LIPL+AHTN+NSD combination (Figure S5h) was associated with a significant delay of cognitive decline in both sexes ($P < 0.001$), with males exhibiting a slower decline relative to females ($P = 0.01$; Table 1). The QuadRx combination (Figure S5i) was associated with a significant delay in cognitive decline in both females and males ($P < 0.001$), which was comparable for both sexes ($P = 0.45$; Table 1).

3.5 | *APOE* genotype differences

Non-treated *APOE* ε4 carriers exhibited accelerated cognitive decline relative to non-carriers ($P < 0.01$; Figure 4A). Change in CDR-SB revealed that untreated *APOE* ε4 carriers exhibited a significantly greater cognitive decline at both 5 and 10 years compared to untreated non-carriers ($P < 0.05$; Figure 4B). In contrast, QuadRx combination at 5 and 10 years mitigated the impact of *APOE* ε4 genotype, such that *APOE* ε4 carriers and non-carriers treated with QuadRx

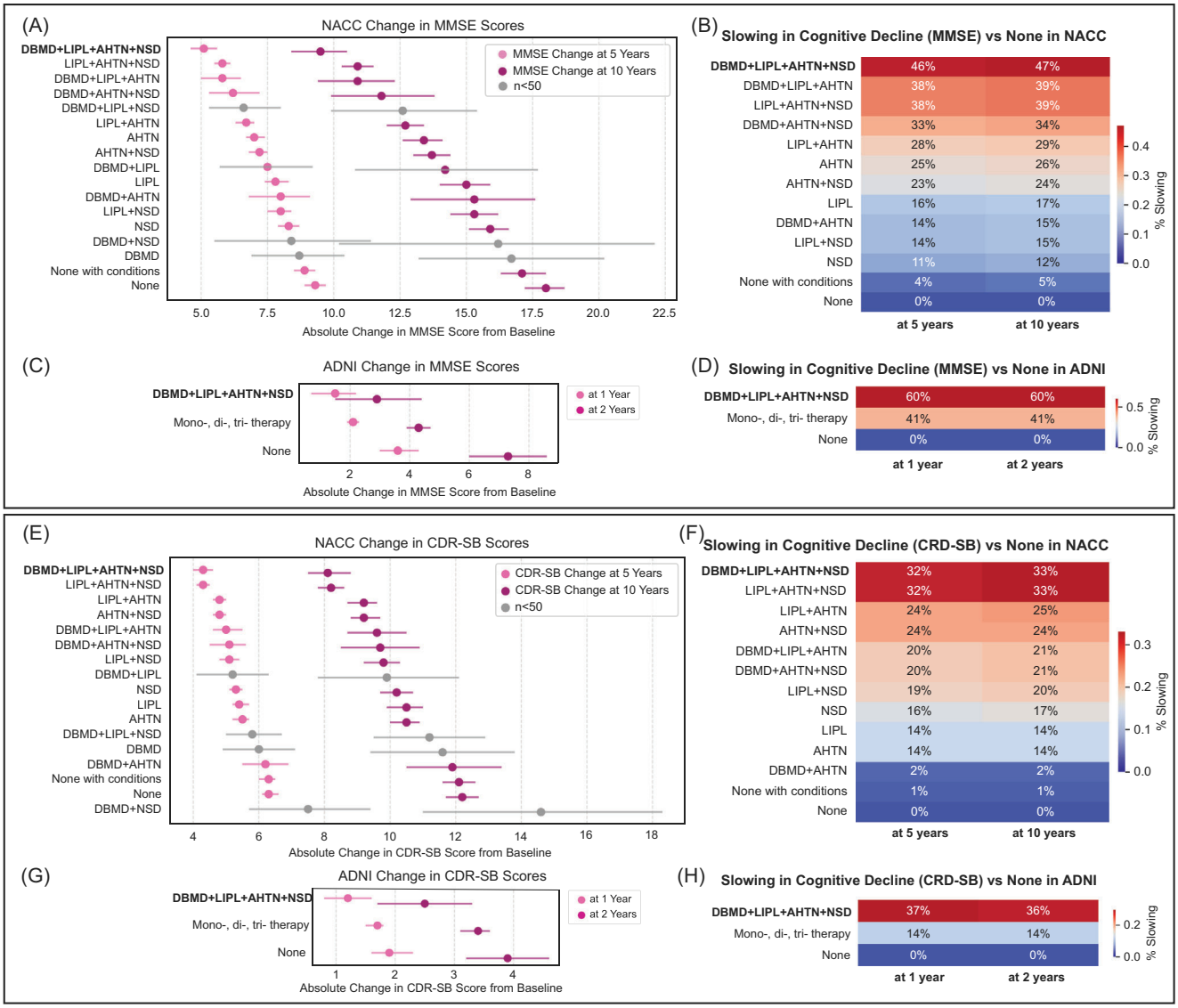

FIGURE 2 Impact of drug combinations on cognitive decline in NACC and ADNI data. A, Change in MMSE scores at 5 and 10 years in NACC participants by therapeutic group. B, Percent of slowing in cognitive decline assessed by MMSE compared to control in NACC data. C, Change in MMSE scores at 1 and 2 years in ADNI participants by therapeutic group. D, Percent of slowing in cognitive decline assessed by MMSE compared to control in ADNI data. E, Change in CDR-SB scores at 5 and 10 years in NACC participants by therapeutic group. F, Percent of slowing in cognitive decline assessed by CDR-SB compared to control in NACC data. G, Change in CDR-SB scores at 1 and 2 years in ADNI participants by therapeutic group. H, Percent of slowing in cognitive decline assessed by CDR-SB compared to control in ADNI data. ADNI, Alzheimer's Disease Neuroimaging Initiative; AHTN, antihypertensive drugs; CDR-SB, *CDR® Dementia Staging Instrument* Sum of Boxes; DBMD, diabetes medication; LIPL, lipid lowering; MMSE, Mini-Mental State Examination; NACC, National Alzheimer's Coordinating Center; NSD, non-steroidal anti-inflammatories.

exhibited a comparable and significant delay in cognitive decline ($P < 0.001$), with *APOE* ε4 carriers performing as well as non-carriers (Figure 4C).

Participants treated with LIPL alone (Figure S6a in supporting information), AHTN alone (Figure S6d), LIPL+AHTN (Figure S6b), LIPL+NSD (Figure S6c), and HTN+NSD (Figure S6e) exhibited significant *APOE* genotype differences ($P < 0.05$), where *APOE* ε4 non-carriers exhibited slower cognitive decline compared to *APOE* ε4 carriers (Table 2). Furthermore, *APOE* ε4 carriers treated with LIPL alone (Table 2, Figure S6a) did not exhibit substantial differences from non-treated participants ($P = 0.39$). However, when these drugs were combined with NSD or AHTN a significant delay of cognitive decline in *APOE* ε4 carriers was evident ($P < 0.001$).

4 | DISCUSSION

The impact of LIPL, DBMD, AHTN, and NSD medications targeting AD risk factors on reducing the risk of developing AD is well documented in observational studies.[14–21] In contrast, randomized clinical trials of the same medications in AD patients who did not have the condition for which the drug was developed (e.g., LIPL use in AD patients without

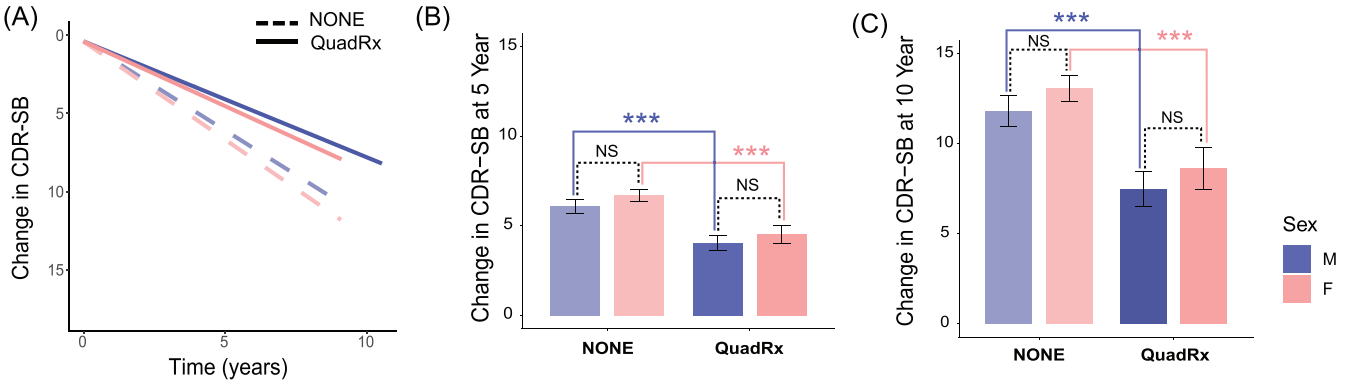

FIGURE 3 Sex differences in CDR-SB score change. A, Change in CDR-SB by sex from baseline over a 10-year period for the quadruplet combination of DBMD+NSD+LIPL+AHTN (QuadRx) and untreated NACC participants (NONE). B, Change in CDR-SB score by sex at 5 years for untreated and QuadRx groups. C, Change in CDR-SB score by sex at 10 years for untreated and QuadRx groups. AHTN, antihypertensive drugs; CDR-SB, *CDR® Dementia Staging Instrument* Sum of Boxes; DBMD, diabetes medication; LIPL, lipid lowering; NACC, National Alzheimer's Coordinating Center; NSD, non-steroidal anti-inflammatories.

TABLE 1 Sex differences in CDR-SB scores at baseline, change in CDR-SB at 5 years, change in CDR-SB at 10 years, and slope of decline between females and males (*P* value) by therapeutic group.

	Baseline		Change from baseline at 5 years		Change from baseline at 10 years		Slope
	Male	Female	Male	Female	Male	Female	
Therapeutic group	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	*p-value*
None	5.6 (5.3–5.9)	5.9 (5.6–6.2)	5.9 (5.6–6.3)	6.5 (6.2–6.8)	11.5 (10.7–12.2)	12.6 (12.0–13.3)	0.02
None with conditions	5.5 (5.1–5.8)	6.0 (5.7–6.3)	6.3 (5.9–6.7)	6.2 (5.9–6.5)	12.3 (11.5–13.0)	12.0 (11.3–12.7)	>0.99
DBMD	6.8 (5.2–8.5)	5.6 (2.9–8.3)	5.2 (3.7–6.7)	6.8 (5.3–8.3)	10.0 (7.0–13.0)	13.2 (10.1–16.3)	0.52
LIPL	5.0 (4.6–5.4)	5.6 (5.2–6.0)	4.9 (4.5–5.3)	6.3 (5.9–6.7)	9.4 (8.6–10.2)	12.2 (11.4–13.1)	<0.001
AHTN	5.6 (5.2–5.9)	6.2 (5.9–6.5)	5.5 (5.2–5.8)	5.5 (5.2–5.8)	10.5 (9.9–11.2)	10.6 (9.9–11.2)	0.92
NSD	5.0 (4.6–5.4)	5.0 (4.6–5.4)	4.8 (4.5–5.2)	5.9 (5.5–6.2)	9.2 (8.5–10.0)	11.3 (10.6–12.0)	<0.001
DBMD+LIPL	5.9 (3.9–8.0)	6.2 (4.8–7.6)	5.3 (3.7–7.0)	5.2 (3.9–6.5)	10.3 (7.0–13.6)	10.1 (7.4–12.7)	>0.99
DBMD+AHTN	6.2 (5.1–7.2)	7.5 (6.3–8.6)	6.5 (5.4–7.6)	6.1 (5.2–7.0)	12.7 (10.5–14.9)	11.8 (9.9–13.6)	0.99
DBMD+NSD	10.1 (6.4–13.7)	3.3 (2.4–4.3)	7.9 (5.7–10.0)	6.6 (3.4–9.7)	15.4 (11.1–19.7)	12.8 (6.4–19.1)	0.72
LIPL+AHTN	4.8 (4.6–5.1)	5.5 (5.2–5.8)	4.9 (4.6–5.2)	4.9 (4.6–5.2)	9.4 (8.8–9.9)	9.4 (8.8–10.0)	0.96
LIPL+NSD	4.8 (4.4–5.2)	4.4 (4.0–4.8)	4.9 (4.6–5.3)	5.5 (5.0–5.9)	9.4 (8.7–10.2)	10.5 (9.7–11.4)	0.24
AHTN+NSD	5.0 (4.6–5.4)	5.4 (5.0–5.8)	4.5 (4.2–4.8)	5.1 (4.8–5.5)	8.6 (8.0–9.3)	9.8 (9.2–10.5)	0.01
DBMD+LIPL+AHTN	5.8 (5.2–6.4)	6.6 (5.9–7.3)	5.1 (4.5–5.8)	5.0 (4.4–5.5)	9.9 (8.5–11.2)	9.6 (8.4–10.8)	>0.99
DBMD+LIPL+NSD	4.7 (3.8–5.7)	5.4 (3.4–7.4)	8.2 (7.0–9.4)	3.9 (2.8–5.1)	16.0 (13.6-18.5)	7.5 (5.2–9.8)	<0.001
DBMD+AHTN+NSD	6.0 (4.7–7.3)	5.6 (3.8–7.4)	3.8 (2.9–4.6)	6.3 (5.5–7.1)	7.1 (5.4–8.8)	12.2 (10.5–13.9)	<0.001
LIPL+AHTN+NSD	4.8 (4.6–5.1)	5.4 (5.1–5.8)	4.2 (4.0–4.5)	4.7 (4.5–5.0)	8.0 (7.6–8.5)	9.0 (8.4–9.6)	0.01
DBMD+LIPL+ AHTN+NSD	4.6 (4.2–5.0)	5.1 (4.5–5.7)	4.1 (3.7–4.5)	4.5 (4.0–5.0)	7.8 (7.0–8.6)	8.7 (7.7–9.7)	0.45

Abbreviations: AHTN, anti-hypertensive; CDR-SB, *CDR® Dementia Staging Instrument* Sum of Boxes; CI, confidence interval; LIPL, lipid lowering; NSD, non-steroidal anti-inflammatory.

dyslipidemia) failed to show clinical benefit.[22–35] Herein, we addressed the hypothesis that AD risk factor therapeutics, when prescribed to AD patients for their intended purpose (e.g., LIPL use in AD patients with dyslipidemia), could exert therapeutic benefits. We tested this hypothesis by conducting longitudinal analyses to assess the association between DBMD, LIPL, AHTN, and NSD use in real-world data (NACC, ADNI) and cognitive decline in AD participants with prescribed therapeutic interventions for their medical indication.

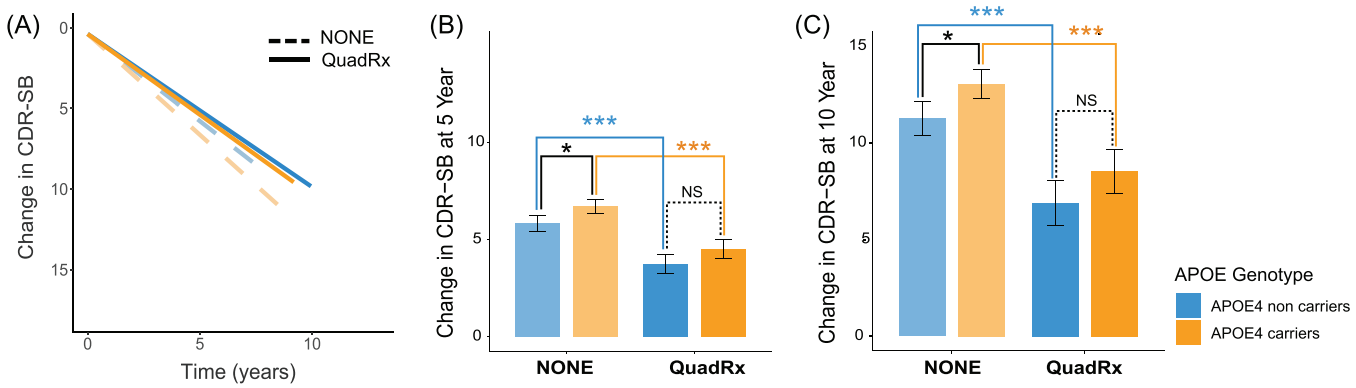

FIGURE 4 *APOE* genotype differences in CDR-SB score change. A, Change in CDR-SB by *APOE* genotype from baseline over a 10-year period for the quadruplet combination of DBMD+NSD+LIPL+AHTN (QuadRx) and untreated NACC participants (NONE). B, Change in CDR-SB score by *APOE* genotype at 5 years for untreated and QuadRx groups. C, Change in CDR-SB score by *APOE* genotype at 10 years for untreated and QuadRx groups. *APOE*, apolipoprotein E; AHTN, antihypertensive drugs; CDR-SB, *CDR® Dementia Staging Instrument* Sum of Boxes; DBMD, diabetes medication; LIPL, lipid lowering; NACC, National Alzheimer's Coordinating Center; NSD, non-steroidal anti-inflammatories.

TABLE 2 *APOE* genotype differences in CDR-SB scores at baseline, change in CDR-SB at 5 years, change in CDR-SB at 10 years, and slope of decline between *APOE* ε4 carriers and non-carriers (*P* value) by therapeutic group.

	Baseline		Change from baseline at 5 years		Change from baseline at 10 years		Slope
	APOE ε4 non-carriers	*APOE* ε4 carriers	*APOE* ε4 non-carriers	*APOE* ε4 carriers	*APOE* ε4 non-carriers	*APOE* ε4 carriers	
Therapeutic group	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	CDR-SB (95% CI)	*p value*
None	5.4 (5.1–5.8)	5.8 (5.4–6.1)	5.8 (5.4–6.2)	6.6 (6.3–6.9)	11.2 (10.4–12.0)	12.8 (12.1–13.5)	<0.001
None with conditions	5.4 (5.1–5.8)	5.6 (5.3–6.0)	6.2 (5.8–6.6)	6.6 (6.3–7.0)	12.0 (11.2–12.8)	12.9 (12.2–13.6)	0.27
DBMD	5.1 (3.9–6.4)	7.2 (3.8–10.6)	6.4 (4.9–8.0)	5.5 (3.9–7.2)	12.5 (9.4–15.6)	10.7 (7.4–14.0)	0.91
LIPL	5.5 (5.0–6.0)	5.1 (4.8–5.5)	4.3 (3.9–4.7)	6.3 (5.9–6.7)	8.3 (7.4–9.1)	12.3 (11.4–13.1)	<0.001
AHTN	5.7 (5.4–6.0)	5.7 (5.4–6.1)	4.6 (4.3–4.9)	6.0 (5.7–6.3)	8.8 (8.2–9.5)	11.6 (10.9–12.2)	<0.001
NSD	4.6 (4.2–5.0)	5.0 (4.7–5.4)	5.1 (4.7–5.5)	5.4 (5.0–5.7)	9.9 (9.1–10.7)	10.4 (9.7–11.1)	0.57
DBMD+LIPL	5.5 (3.7–7.3)	5.9 (4.7–7.1)	6.2 (4.5–8.0)	5.0 (3.6–6.4)	12.1 (8.6–15.7)	9.6 (6.7–12.5)	0.69
DBMD+AHTN	6.4 (5.3–7.5)	7.0 (5.5–8.5)	7.9 (6.8–8.9)	5.8 (4.8–6.9)	15.4 (13.3–17.6)	11.3 (9.2–13.4)	0.04
DBMD+NSD	5.2 (3.1–7.3)	6.3 (−0.5–13.2)	8.7 (6.2–11.2)	3.1 (−0.6,6.8)	17.1 (12.1–22.0)	5.8 (−1.5–13.2)	0.07
LIPL+AHTN	4.9 (4.6–5.2)	5.1 (4.9–5.4)	4.5 (4.2–4.8)	5.1 (4.8–5.3)	8.6 (7.9–9.3)	9.7 (9.1–10.3)	0.04
LIPL+NSD	4.4 (3.9–4.9)	4.6 (4.2–5.0)	4.5 (4.1–5.0)	5.5 (5.1–5.9)	8.7 (7.8–9.6)	10.6 (9.8–11.3)	<0.01
AHTN+NSD	5.1 (4.7–5.5)	4.8 (4.4–5.2)	4.5 (4.1–4.8)	5.0 (4.7–5.3)	8.4 (7.8–9.1)	9.4 (8.8–10.1)	0.09
DBMD+LIPL+AHTN	6.2 (5.5–6.9)	5.4 (4.8–6.1)	4.8 (4.1–5.5)	5.3 (4.6–6.0)	9.2 (7.9–10.6)	10.2 (8.8–11.6)	0.85
DBMD+LIPL+NSD	4.2 (2.3–6.1)	4.7 (3.7–5.6)	5.1 (3.9–6.3)	7.0 (5.7–8.2)	9.8 (7.4–12.2)	13.6 (11.1–16.1)	0.11
DBMD+AHTN+NSD	5.5 (4.0–7.0)	5.7 (4.0–7.4)	4.6 (3.7–5.4)	6.1 (5.2–7.0)	8.8 (7.1–10.5)	11.8 (10.0–13.7)	0.07
LIPL+AHTN+NSD	4.8 (4.5–5.1)	4.9 (4.7–5.2)	4.4 (4.1–4.7)	4.4 (4.1–4.6)	8.3 (7.7–8.9)	8.2 (7.8–8.7)	>0.99
DBMD+LIPL+ AHTN+NSD	4.6 (4.0–5.1)	5.1 (4.5–5.7)	3.8 (3.3–4.3)	4.5 (4.1–5.0)	7.2 (6.2–8.2)	8.7 (7.7–9.7)	0.12

Abbreviations: AHTN, anti-hypertensive; CDR-SB, *CDR® Demential Staging Instrument* Sum of Boxes; CI, confidence interval; LIPL, lipid lowering; NSD, non-steroidal anti-inflammatory.

NACC analyses revealed that 74% of AD participants were treated with at least one therapeutic, consistent with the prevalence of risk factors driving AD development.[1–3] Furthermore, 61% of treated participants received drug combinations, which is consistent with multiple systems of biology associated with the risk of AD.

Outcomes of NACC analyses indicated that the impact of therapeutics on delay in cognitive decline was evident in monotherapy, di-therapies, tri-therapies, and was greatest in quadruplet therapies (QuadRx). Monotherapy of LIPL, AHTN, or NSD was significantly correlated with delayed cognitive decline assessed by MMSE and CDR-SB

(12% to 26%) compared to untreated participants at 10 years. Surprisingly, participants treated for the greatest number of comorbidities (QuadRx) exhibited greatest delay in cognitive decline (47% MMSE and 33% CDR-SB at 10 years). Combinations of two or three drugs were associated with a significant delay of cognitive decline, ranging from 15% to 39%. These outcomes were confirmed in ADNI, in which mono-, di-, or tri- combinations resulted in a significant 41% delay in cognitive decline with the greatest delay evident for QuadRx-treated participants (60% MMSE and 36% CDR-SB).

Notably, NACC and ADNI participants on combination therapies had better cognitive performance at baseline but were older at the time of enrollment. These findings are consistent with combination therapy sustaining cognitive function in those at risk for AD and delaying age of onset.[14–21]

The NONE with conditions group had the lowest mortality rate (38.7% of participants died between follow-up visits vs. 61.3% overall). These participants reported a history of AD risk factors that were not pharmacologically treated, possibly due to the mild nature of their conditions, which could have been managed through lifestyle interventions. In contrast, NONE participants—who did not report any conditions—had a higher mortality rate (59.6%). Differences in mortality rate did not impact the primary findings, as assessed in secondary analyses excluding participants who died between follow-up visits.

Sex and *APOE* genotype both impacted the magnitude of cognitive decline, which replicates previous findings that identified subsets of responders based on sex and *APOE* genotype within unsuccessful clinical trials of these therapies.[36–38] *APOE* ε4 carriers exhibited the greatest cognitive benefit of QuadRx.

NACC strengths include longitudinal cognitive assessments by sex and *APOE* genotype that extend to 10 years of follow-up with medical history and associated medications. Limitations of both NACC and ADNI datasets include (1) self-reported medication use, (2) classification of drugs into therapeutic groups which precludes the ability to categorize medications based on mechanism of action within a drug class, and (3) number of participants within different therapeutic groups. While ADNI had fewer participants than NACC, they were more deeply phenotyped for AD, older, and more cognitively impaired but still confirmed NACC findings. One limitation is potential overlap of participants between NACC and ADNI datasets, which Health Insurance Portability and Accountability Act regulations prohibit identifying. While overlap is possible, these datasets are independently collected with different methodologies, clinical settings, and baseline characteristics. ADNI participants were older and exhibited more severe cognitive impairment at baseline compared to NACC participants. Furthermore, the frequency of *APOE* ε4 carriers and medication distribution was different between the two cohorts, supporting their independence. Replication of findings across these datasets, despite these differences, supports the robustness of observed associations. Moreover, if substantial overlap influenced findings, disease trajectories would converge, yet both datasets exhibited distinct cognitive decline patterns, reinforcing the validity of ADNI as an independent cohort.

Although use of both MMSE and CDR-SB provides a comprehensive assessment of functional and cognitive domains, these tests have several limitations such as limited data on psychometric properties, cultural and educational bias, or ceiling and floor effects, among others.[41,45] Further studies should include validated AD blood-based biomarkers and neuroimaging outcomes in addition to educational and diversity measures in larger comprehensive datasets.

Clinical translation of QuadRx therapeutic benefit to slow cognitive decline is limited to those who have the medical condition for which the therapy was developed. This conclusion aligns with results from multiple failed clinical trials involving persons who did not have the underlying clinical condition for which the drug was intended.[22–35]

Overall, findings reported herein indicate that targeting multiple systems of biology driving development and progression of AD significantly delays cognitive decline in participants with AD risk factors. The delay in cognitive decline in treated AD participants indicated that mechanisms driving these AD risk factors not only increase the risk of AD but exert an active role in its progression. While treating these AD risk factors slows cognitive decline, these therapies either alone or in combination do not halt or reverse cognitive decline, which indicates AD-specific mechanisms that remain to be identified and therapeutically targeted. Targeting one system with one medication can slow cognitive decline, whereas targeting multiple systems that contribute to AD with a combination of mechanism-specific therapies can exert greater delay in progression. Rather than acting as a direct disease-modifying intervention for AD, QuadRx represents a comprehensive strategy for managing multiple independent risk factors that contribute to cognitive decline.

The magnitude of delay in CDR-SB decline of QuadRx (2 years: NACC 29%/ADNI 36%) was comparable to, if not greater than, approved amyloid antibodies lecanemab (18 months: 27%[7]) and aducanumab (78 weeks: 22%[8]). Notably, lecanemab and aducanumab clinical trial participants were younger and had higher baseline cognition compared to NACC and ADNI participants.[7,8] Further, QuadRx was equally effective in females and males whereas lecanemab was not effective in females.[7] Given the heterogeneity of AD patients[46] and that a small fraction meet clinical criteria for amyloid-targeted antibody treatment,[47] the need for alternative disease-modifying strategies with well-established safety profiles in diverse populations is highly relevant.

Delaying the rate of cognitive decline has clinical benefits for AD patients and could extend a window of therapeutic opportunity for the reversal of disease. Importantly, QuadRx was associated with a significant slowing of cognitive decline over a 5-year period, resulting in a lower rate of progression from mild to moderate dementia.[42] Specifically, at the 5-year assessment point, participants treated with QuadRx exhibited a 32% reduction in cognitive decline in CDR-SB compared to untreated participants, which could extend the window of independent living.[48] Outcomes of precision combination therapies based on sex and *APOE* genotype that effectively and safely slow the rate of cognitive decline could alter the course of AD and burden of care.

AUTHOR CONTRIBUTIONS

Formal analysis (lead): Yuan Shang and Georgina Torrandell-Haro. Methodology (lead): Yuan Shang. Writing-original draft (lead): Yuan Shang and Georgina Torrandell-Haro. Methodology (supporting): Georgina Torrandell-Haro, Francesca Vitali. Writing-original draft (supporting): Francesca Vitali. Writing-review & editing (equal): Francesca Vitali, Roberta Diaz Brinton. Supervision (equal): Roberta Diaz Brinton. Conceptualization (lead): Roberta Diaz Brinton. Funding acquisition (lead) and supervision (lead): Roberta Diaz Brinton.

ACKNOWLEDGMENTS

Research reported herein was supported by the National Institute on Aging (grants 5R01AG057931-02 [Sexd Differences in Molecular Dementias of Alzheimer's Disease Risk: Prodromal Endophenotype], P01AG026572 [Perimenopause in Brain Aging and Alzheimer's Disease]), the Alzheimer's Drug Discovery Foundation to Roberta Diaz Brinton, and the University of Arizona Center for Innovation in Brain Science. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

The databases used in this study are available from: National Alzheimer's Coordinating Center (NACC, https://naccdata.org/, data version v62) and Alzheimer's Disease Neuroimaging Initiative (ADNI, https://adni.loni.usc.edu/, data accessed at May 9, 2024). These data are available upon request.

ETHICS STATEMENT

This study is a retrospective study and was conducted using de-identified data provided by the National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI). No institutional review board was necessary as all data from NACC and ADNI was de-identified and there was no patient involvement in the study, its design, recruitment, or the outcomes. Data are publicly available with subscription at https://naccdata.org/ and https://adni.loni.usc.edu/data-samples/access-data/.

CONSENT STATEMENT

No additional data were collected from participants without their informed consent.

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SUPPORTING INFORMATION

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

How to cite this article: Shang Y, Torrandell-Haro G, Vitali F, Brinton RD; for The Alzheimer's Disease Neuroimaging Initiative (ADNI). Combination therapy targeting Alzheimer's disease risk factors is associated with a significant delay in Alzheimer's disease–related cognitive decline. *Alzheimer's Dement*. 2025;11:e70074. https://doi.org/10.1002/trc2.70074