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RESEARCH ARTICLE

Association between the use of levodopa/carbidopa, Alzheimer's disease biomarkers, and cognitive decline among participants in the National Alzheimer's Coordinating Center Uniform Data Set

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Abstract

INTRODUCTION: This retrospective study investigates whether exposure to levodopa/carbidopa (LA/CA) medication is associated with modified Alzheimer's disease (AD) trajectories.

METHODS: Multivariate analysis used cerebrospinal fluid (CSF) biomarker information included in the National Alzheimer's Coordinating Center Uniform Data Set for subjects with normal cognition (NC), mild cognitive impairment (MCI), and dementia (DE). Survival analyses examined the progression to MCI/DE and death events.

RESULTS: LA/CA use is associated with lower levels of CSF amyloid beta, phosphorylated-tau (p-tau) and total-tau. After adjusting for age, sex, and apolipoprotein E (APOE) $\varepsilon 4$ allele presence, that effect was quantified by negative coefficients of the fitted linear mixed models: p-values < 0.01 in all cases except for p-tau in the MCI subgroup ($p = 0.02$). No similar effects were identified for other antiparkinsonians. Exposure to LA/CA decreased the progression from MCI to DE ($p = 0.03$).

DISCUSSION: The identified association between LA/CA exposure, AD biomarkers, and progression deserves further investigation in controlled clinical trials.

KEYWORDS
Alzheimer's disease, carbidopa, cerebrospinal fluid biomarkers, dopamine, levodopa, mild cognitive impairment

Highlights

- LA/CA is associated with lower levels of CSF biomarkers for AD.
- This effect is not observed when other antiparkinsonian drugs are used.
- LA/CA is also associated with delayed progression to dementia by AD patients with MCI.

1 | BACKGROUND

Alzheimer's disease (AD) is clinically characterized by progressive cognitive decline and memory loss. While the primary pathological hallmarks of AD are amyloid beta (Aβ) plaques and tau neurofibrillary tangles, the balance of neurotransmitters such as acetylcholine, glutamate, serotonin, and dopamine is significantly affected in the AD brain.[1] In particular, molecular neuroimaging studies of the dopaminergic vulnerability in AD patients confirm that the ventrotegmental-mesocorticolimbic pathway is already affected in the prodromal stages of the disease.[2] A link between the pathophysiology of AD and dopamine deficiency is also suggested by a network meta-analysis of data from a total of 512 AD patients and 500 healthy controls[3] and by preclinical studies using, for example, the TgF344 rat, 3xTg-AD mouse, Tg2576 mouse, and 5xFAD mouse models of AD.[4–6] Protecting the dopaminergic system emerges, therefore, as a possible hypothesis for AD therapy.[7]

Levodopa (L-3,4-dihydroxyphenylalanine, L-DOPA) is a dopamine precursor that, unlike dopamine, is able to cross the blood–brain barrier. Orally administered levodopa can be prematurely converted into peripheral dopamine by the aromatic L-amino acid decarboxylase (AADC) enzyme. Combining levodopa with the AADC inhibitor carbidopa greatly increases the amount of levodopa available to the brain. Levodopa/carbidopa (LA/CA) medication is used in the context of Parkinson's disease (PD) to treat motor symptoms caused by dopamine deficiency. LA/CA can also be prescribed to AD patients who manifest Parkinsonian signs in addition to the behavioral and psychological symptoms characteristic of AD. Despite the beneficial effects of levodopa observed using animal models of AD,[6,8–10] an assessment of the clinical effects of dopaminergic drugs on AD outcomes is currently lacking in the literature.

Dopamine agonists can be used either as adjunctive therapy or as levodopa-sparing agents to mimic the action of dopamine in stimulating striatal post-synaptic receptors.[11] In fact, long-term treatments with levodopa are associated with motor complications such as delayed on or wearing off phenomena.[11,12] Dopamine agonists such as pramipexole, ropinirole, and rotigotine have replaced levodopa as the first-line treatment of restless leg syndrome,[13] a neurological disorder characterized by dopamine dysregulation rather than dopamine deficiency.[14]

The National Alzheimer's Coordinating Center (NACC) developed and maintains the Uniform Data Set (UDS) of clinical information that has been collected from Alzheimer's Disease Research Centers in the United States since 2005.[15] Among several other records, the UDS includes follow-ups of the clinical diagnosis and prescribed medication and, in some cases, imaging and cerebrospinal fluid (CSF) biomarker data and the genetic characterization of the apolipoprotein E (APOE) genotype. Using the NACC-UDS resource, relationships have been established between CSF biomarkers, neuropsychiatric symptoms, and trajectories of depression/apathy,[16,17] patients misdiagnosed with AD and their medication use,[18] metformin use and the risk of severe dementia in AD patients with type 2 diabetes,[19] and vitamin D supplementation and dementia incidence rates,[20] among others.[15]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources such as PubMed and Google Scholar. While dopamine deficiency has been linked to the pathophysiology of AD, the relationship between the use of dopamine-restoring medication and AD outcomes has not been widely studied at the clinical level.
2. **Interpretation**: Our analysis of the NACC UDS suggests disease-modifying effects of LA/CA medication in lowering CSF levels of CSF biomarkers for AD and delaying the progression to dementia in AD patients with MCI.
3. **Future directions**: This observational and exploratory study deserves further investigation on the pros and cons of LA/CA use by AD patients showing no Parkinsonian symptoms. Since the dopaminergic system is also affected in AD, dose-adjusted LA/CA drugs are conceived as possible approaches to correct mild dopamine deficiency and delay the progression of AD.

NACC participants are subject to annual clinical, neurological, and neuropsychological diagnoses of normal cognition (NC), mild cognitive impairment (MCI), impaired-not-MCI, or dementia (DE) using as criteria the presence of a subjective cognitive complaint, objective impairment on a cognitive test, and deficits in everyday functioning.[21] APOE genotype is available for a large number of participants (>75%).[22] CSF values for amyloid beta (Aβ42), total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau) are available on a subset of UDS participants. Concerning these AD biomarkers, it is generally considered that CSF Aβ42 levels are negatively correlated with amyloid load in the brain,[23] whereas t-tau and p-tau levels are positively correlated with neuronal damage and neurodegeneration.[24]

Here, we analyzed the CSF biomarker data and clinical trajectory of NACC-UDS participants who were prescribed LA/CA. Our goal was to investigate whether AD outcomes were affected by exposure to LA/CA while accounting for important variables such as the baseline diagnosis of dementia, subject demographics, and the presence of APOE allele ε4. Subgroups of individuals with NC, MCI, and DE were separately assessed for the levels of CSF Aβ42, t-tau, and p-tau. A hypothetical disease-progression effect of LA/CA was further tested by analyzing the probabilities of survival to cognitive decline and death events calculated for subjects with and without a history of LA/CA use. We found that LA/CA exposure was associated with lowered levels of all CSF biomarkers and delayed progression from MCI to DE.

2 | METHODS

2.1 | Participants

The participants in this study were those included in the subset of the (de-identified) NACC UDS sample (March 2024 data freeze) who

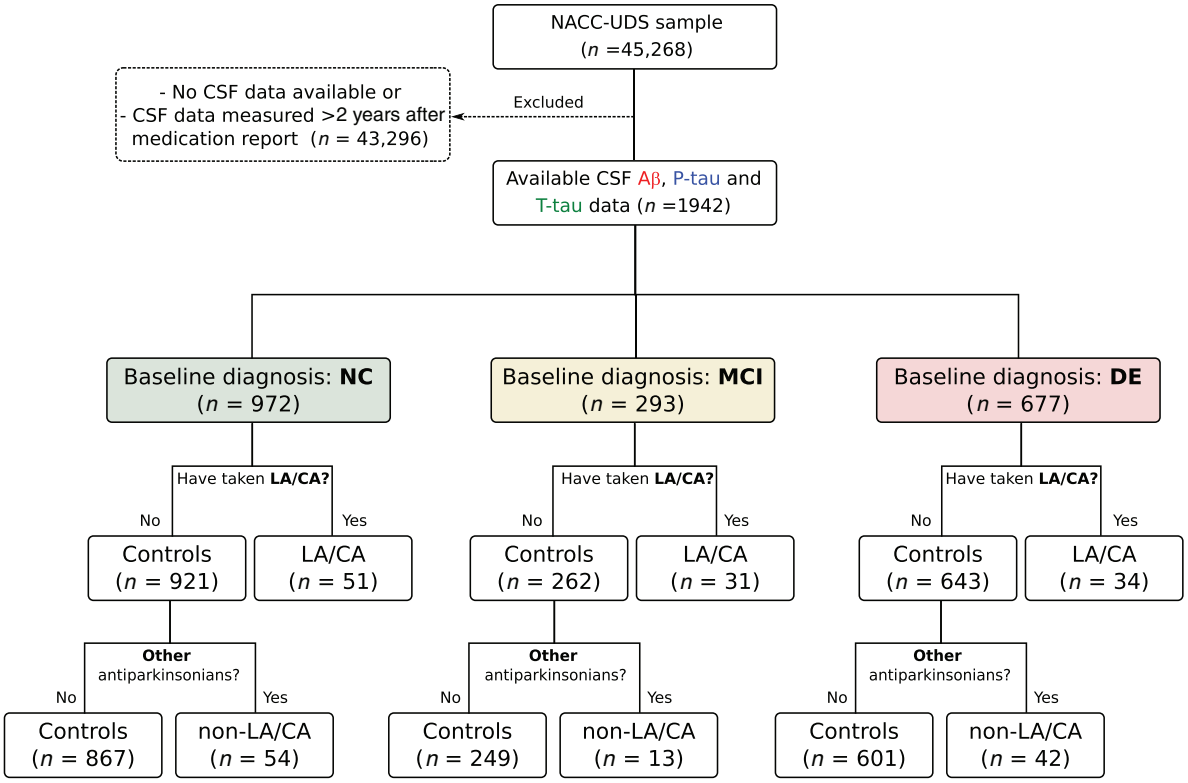

FIGURE 1 Flow chart of subject selection for multivariate analyses of CSF biomarker data in NC, MCI, and DE subgroups exposed to LA/CA or other antiparkinsonian drugs and controls. CSF, cerebrospinal fluid; DE, dementia; LA/CA, levodopa/carbidopa; MCI, mild cognitive impairment; NC, normal cognition.

allowed the sharing of research data with commercial entities. The NACC program was developed to facilitate collaborative involvement among Alzheimer's Disease Research Centers (ADRCs) in the United States. In 2005, ADRCs began collecting longitudinal demographic, clinical, neuropsychological, and diagnostic data using Version 1 of the dataset, which was subsequently updated and expanded with the implementation of Versions 2 (2008) and 3 (2015) of the UDS.[15,25] The UDS Version 3 is non-proprietary (available upon a data request) and provides a standardized methodology for assessing cognition and clinical characteristics of patients with AD and other neurological diseases.[15] Each ADRC enrolls its participants according to its protocols, for example, through clinician referral, self-referral by participants or family members, and active recruitment in community organizations. This longitudinal protocol requires annual follow-up while the participant is able and willing to be involved and comprises eight data-collection forms that are completed by clinicians or clinical staff in each ADRC (https://naccdata.org).

2.2 | Definition of cases and controls

Our study was divided into a multivariate analysis of CSF biomarker data and a survival analysis of disease progression data. Cases for which the baseline characterization of prescribed medication occurred more than 2 years after the CSF test were excluded (Figure 1). Results from at least one CSF test were available for 1942 subjects comprising the clinical subgroups diagnosed at the baseline with NC (972), MCI (293), and DE (677). For each clinical subgroup, LA/CA cases and controls were defined according to the absence (controls) or existence (cases) of reported use of levodopa or carbidopa medication. This criterion comprises current or past prescriptions of clinical drugs whose names include the words "levodopa" or "carbidopa" in any of the 40 "DRUG" fields of UDS form A4. In an additional multivariate analysis, the population of LA/CA controls, that is, participants who do not have reported use of LA/CA, were further divided into those who did (cases) or did not (controls) take any of the following non-LA/CA antiparkinsonian drugs: "pramipexole," "ropinirole," "bromocriptine," "pergolide," "cabergoline," "tolcapone," "rotigotine," "entacapone," or "rasagiline" (Figure 1). Table S1 shows the drug names and brands of the antiparkinsonian agents considered in the NACC UDS study. Each clinical subgroup was characterized in terms of a number of cases of parkinsonian symptoms reported as PD, other parkinsonian disorder, parkinsonian signs, or parkinsonian gait disorder. In the survival analysis of cognitive decline (Figure 2), subjects diagnosed with NC (13,442) or MCI (6906) at baseline were divided into LA/CA cases and controls following the same criterion as in the multivariate analysis discussed earlier. Then nearest-neighbor 1:1 matching was performed to obtain equally sized LA/CA-exposed and LA/CA-naive samples in all NC and MCI groups. Disease progression was also characterized in terms of the probability of death events in the NC and

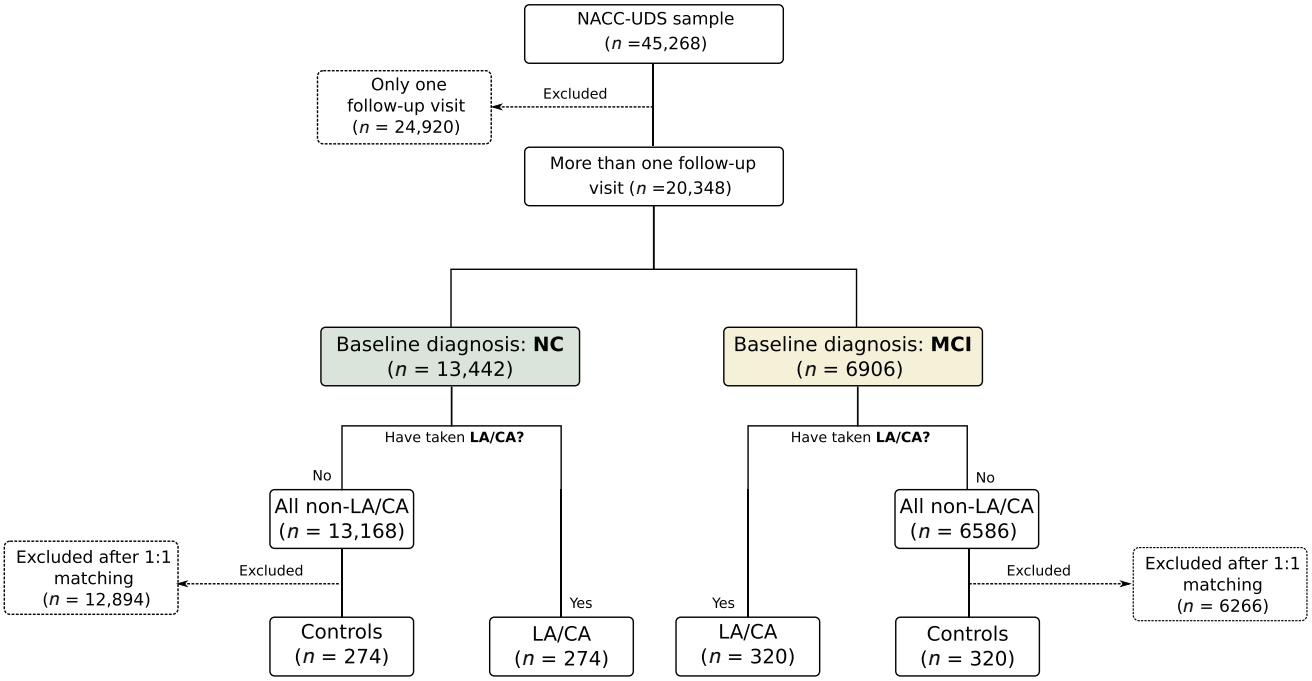

FIGURE 2 Flow chart of subject selection for analyses of cognitive decline by NC and MCI subgroups exposed to LA/CA and controls. LA/CA, levodopa/carbidopa; MCI, mild cognitive impairment; NC, normal cognition.

MCI groups and in an additional group of subjects diagnosed with DE at baseline.

2.3 | Study variables

The multivariate analyses used as dependent and continuous variables each of the CSF levels of Aβ42, t-tau, and p-tau measured using enzyme-linked immunosorbent assay (ELISA) or Luminex multiplex xMAP assay protocols. Disease progression analyses used cognitive decline data obtained after clinical evaluation or the information of death events reported to NACC. Baseline and follow-up stratifications between NC, MCI, and DE cases followed the same criteria as those adopted by previous authors.[26] The main covariates considered in our study were, for each clinical subgroup, age, sex, and the presence of APOE allele ε4. Here, "APOE ε4 carriers" classify the presence of APOE ε3/ε4, ε4/ε4, or ε4/ε2 genotypes. We also collected information about the education level (in years), race (grouped as White, Black or African American, and others), comorbidities such as hypertension, cardiovascular disease, and cancer, and concurrent medication such as non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, antipsychotics, hormones, antihypertensives, diabetes medication, lipid-lowering medication, and antidepressants.

2.4 | Statistical analysis

Unless stated otherwise, the two-sided unpaired *t*-test or the Fisher test were carried out using the "ttest2" or "fishertest" function of MATLAB R2023a (MathWorks, Natick, MA, USA) for comparisons between two groups of continuous variables or categorical variables, respectively. In our multivariate analysis, a linear mixed-effects (LME) model regression was performed to determine if the levels of CSF Aβ42, t-tau, and p-tau were significantly affected by LA/CA use in the NC, MCI, and DE subgroups. The adopted Wilkinson notation was the following: BIOMARKER~TREATMENT+AGE+SEX+APOE+(1|PATIENT), where BIOMARKER is the continuous variable corresponding to the CSF levels for each biomarker, TREATMENT denotes whether or not the patient was exposed to LA/CA, AGE, SEX, and APOE are additional covariates, and 1|PATIENT denotes random intercepts assigned to individual patients. For the sake of a balanced missing data pattern, observations with at least one of the CSF levels missing were eliminated, thereby ensuring equally sized Aβ42, t-tau, and p-tau samples. The LME model was regressed using the "fitlme" function of MATLAB R2023a (MathWorks, Natick, MA) to determine LME coefficients (β) and the associated *p*-values; then the "coefTest" function was used to test whether all fixed-effects coefficients except the intercept were 0. In the survival analysis, the Kaplan–Meier method was used to determine the cumulative probabilities of (1) cognitive decline from NC to MCI/DE or from MCI to DE and (2) the occurrence of death events in each clinical subgroup. Next, we performed propensity score matching and log-rank (Mantel-Cox) tests to quantify the magnitude of the LA/CA effect. First, the "NearestNeighbors.fit()" function from the scikit-learn Python package was used for automatic 1:1 nearest-neighbor matching by "age," "sex," and "APOE ε4." This procedure warrants uniform sampling and random distribution of unreported cases of death events or LA/CA use. GraphPad Prism software (La Jolla, CA, USA) was then used to determine *p*-values for each comparison of survival curves. All comparisons were performed between two groups

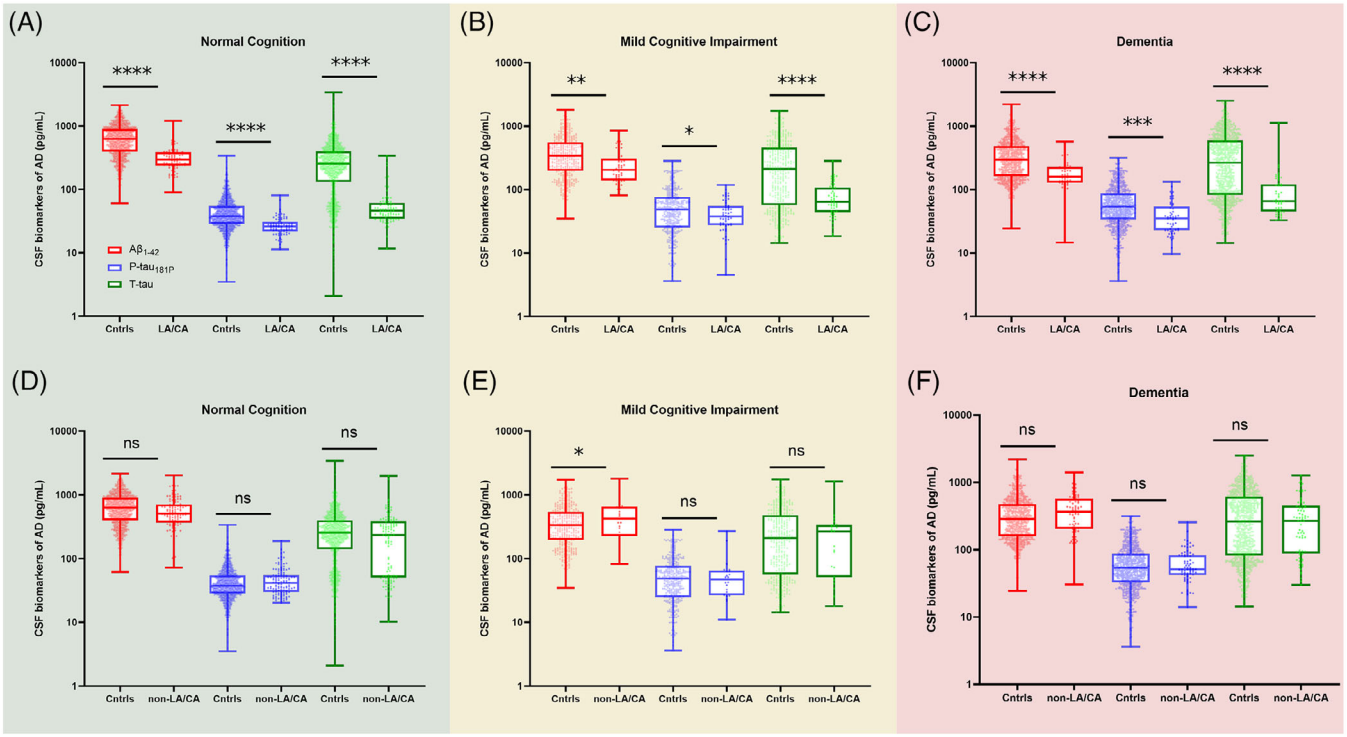

FIGURE 3 Association between use of (top) LA/CA and (bottom) non-LA/CA antiparkinsonian drugs and the levels of CSF biomarkers for AD. Boxplots of measured levels of CSF Aβ42 (red), P-tau (blue), and T-tau (green) for the (A and D) NC, (B and E) MCI, and DE (C and F) subgroups. The boxes extend from the 25th to 75th percentiles, the central line is the median, and the whiskers represent minimum and maximum values. Stars show the statistical significance of differences between controls and cases quantified by LME model regression, with more stars indicating lower *p*-values associated with the variable "TREATMENT" in Table 2. A number of CSF tests: (A) 1481 controls and 79 LA/CA cases; (B) 377 controls and 54 LA/CA cases; (C) 886 controls and 53 LA/CA cases; (D) 1358 controls and 117 LA/CA cases; (E) 354 controls and 23 LA/CA cases; (E) 812 controls and 73 LA/CA cases. CSF, cerebrospinal fluid; DE, dementia; LA/CA, levodopa/carbidopa; LME, linear mixed-effects; MCI, mild cognitive impairment; NC, normal cognition.

only (cases and controls) so that multiple hypothesis corrections, using, for example, the Bonferroni and Holm-Sidak methods, were not required. *p*-values less than 0.05 were considered significant.

3 | RESULTS

3.1 | Association between use of LA/CA and CSF biomarker levels

LA/CA use was associated with lower levels of Aβ42, t-tau, and p-tau in the CSF of subjects diagnosed at baseline with NC, MCI, or DE (Figure 3, top). Although the populations of cases and controls were heterogeneously affected by different covariates (Table 1, top), the lowering effect of LA/CA on CSF biomarker levels was confirmed by LME model regressions adjusted for the effects of variables "age," "sex," and "APOE ε4 allele" (Table 2, top). Statistically significant effects were also invariably observed for the APOE covariate in decreasing CSF Aβ42 levels and increasing CSF t-tau and p-tau. For all CSF biomarkers and all clinical subgroups, the robustness of the LME regression was additionally confirmed by post hoc *F* tests (*p*-values always below 3×10^{-5}) and by interaction analysis between variable "treatment" and all other variables (Table S2). The effects of the "age" variable in increasing CSF t-tau and p-tau were statistically significant in all subgroups except DE. In our study, the "sex" variable had no significant effect on biomarker levels except for CSF Aβ42 in the DE subgroup (CSF Aβ42 levels are lower in females diagnosed with DE). The percentages of subjects with reported parkinsonian symptoms in the LA/CA cases/control groups were 27.4%/0.5% (NC), 32.2%/5.0% (MCI), and 14.7%/6.7% (DE).

We tested whether the correspondence between lowered levels of AD biomarkers and LA/CA use would also be observed in subjects prescribed dopamine agonists or other dopaminergic drugs distinct from LA/CA. None of the effects reported for LA/CA could be observed in the groups subject to levodopa-sparing treatments. No significant effect of non-LA/CA antiparkinsonian drugs was identified on the levels of CSF t-tau and p-tau in any of the subgroups NC, MCI, or DE, while the CSF Aβ42 levels were increased (rather than decreased) in one of the subgroups (Figure 3, bottom). As with the LA/CA results, a multivariate analysis adjusted for the variables "age," "sex," and "APOE ε4 allele" was performed to account for the heterogeneous populations of cases and controls (Table 1, bottom). Again, APOE ε4 carriers had systematically lower CSF Aβ42 and higher t-tau and p-tau levels, while older subjects of the subgroups NC and MCI tended to have higher

TABLE 1 Characteristics of participants exposed to antiparkinsonian drugs (LA/CA, non-LA/CA, and controls) in CSF biomarker study.

	NC			MCI			DE		
Variable	**Controls**	**Cases**	***p*-value**	**Controls**	**Cases**	***p*-value**	**Controls**	**Cases**	***p*-value**
Levodopa/carbidopa (LA/CA)									
n	921	51		262	31		643	34	
Female *n* (%)	517 (56.1)	20 (39.2)	0.021	108 (41.2)	5 (16.1)	0.006	293 (45.6)	19 (55.9)	0.29
Age	70 (9)	67.3 (12)	0.037	71.6 (9.1)	70.4 (8.4)	0.471	71.4 (9.4)	71.6 (10.9)	0.883
APOE ε4, *n* (%)	338 (36.7)	12 (23.5)	0.071	122 (46.6)	13 (41.9)	0.705	336 (52.3)	16 (47.1)	0.6
Acation level (years)	16.2 (4.7)	15.9 (2.4)	0.614	16 (6.2)	16.3 (2.7)	0.837	15.4 (7.4)	14.6 (4.4)	0.542
Race/White, *n* (%)	822 (89.3)	48 (94.1)	0.352	236 (90.1)	29 (93.5)	0.751	581 (90.4)	30 (88.2)	0.564
Race/Black or African American, *n* (%)	80 (8.7)	1 (2)	0.116	13 (5)	1 (3.2)	1	39 (6.1)	1 (2.9)	0.714
Race/Other, *n* (%)	19 (2.1)	2 (3.9)	0.303	13 (5)	1 (3.2)	1	23 (3.6)	3 (8.8)	0.137
Hypertension, *n* (%)	394 (42.8)	15 (29.4)	0.079	135 (51.5)	14 (45.2)	0.571	285 (44.3)	15 (44.1)	1
Cardiovascular disease, *n* (%)	62 (6.7)	9 (17.6)	0.009	23 (8.8)	3 (9.7)	0.746	55 (8.6)	5 (14.7)	0.213
Cancer, *n* (%)	32 (3.5)	0 (0)	0.406	11 (4.2)	0 (0)	0.613	19 (3)	0 (0)	0.617
NSAIDs, *n* (%)	379 (41.2)	7 (13.7)	0	110 (42)	7 (22.6)	0.051	219 (34.1)	6 (17.6)	0.06
Anticoagulant or antiplatelet agent, *n* (%)	379 (41.2)	7 (13.7)	0	110 (42)	7 (22.6)	0.051	219 (34.1)	6 (17.6)	0.06
Antipsychotic agent, *n* (%)	11 (1.2)	1 (2)	0.478	12 (4.6)	3 (9.7)	0.203	36 (5.6)	2 (5.9)	1
Hormone therapy, *n* (%)	44 (4.8)	1 (2)	0.508	8 (3.1)	0 (0)	1	13 (2)	1 (2.9)	0.517
Antihypertensive or blood pressure, *n* (%)	427 (46.4)	21 (41.2)	0.564	148 (56.5)	15 (48.4)	0.446	317 (49.3)	19 (55.9)	0.486
Diabetes medication, *n* (%)	65 (7.1)	5 (9.8)	0.406	38 (14.5)	6 (19.4)	0.434	54 (8.4)	5 (14.7)	0.207
Lipid-lowering medication *n* (%)	366 (39.7)	15 (29.4)	0.184	120 (45.8)	14 (45.2)	1	288 (44.8)	14 (41.2)	0.726
Antidepressant *n* (%)	221 (24)	10 (19.6)	0.612	103 (39.3)	12 (38.7)	1	265 (41.2)	14 (41.2)	1
Other Antiparkinsonians (non-LA/CA)									
n	867	54		249	13		601	42	
Female, *n* (%)	492 (56.7)	25 (46.3)	0.157	99 (39.8)	9 (69.2)	0.044	272 (45.3)	21 (50)	0.631
Age	70.1 (9)	69.3 (7.9)	0.537	71.7 (9)	71.5 (12.4)	0.945	71.4 (9.5)	71.2 (8.3)	0.883
APOE ε4, *n* (%)	312 (36)	26 (48.1)	0.081	116 (46.6)	6 (46.2)	1	312 (51.9)	24 (57.1)	0.528
Education level (years)	16.2 (4.8)	16.3 (2.8)	0.878	15.7 (3.4)	21.7 (23.4)	0.001	15.2 (6.8)	17.3 (13.4)	0.078
Race/White, *n* (%)	773 (89.2)	49 (90.7)	1	223 (89.6)	13 (100)	0.375	540 (89.9)	41 (97.6)	0.169
Race/Black or African American, *n* (%)	77 (8.9)	3 (5.6)	0.616	13 (5.2)	0 (0)	1	39 (6.5)	0 (0)	0.101
Race/Other, *n* (%)	17 (2)	2 (3.7)	0.307	13 (5.2)	0 (0)	1	22 (3.7)	1 (2.4)	1
Hypertension, *n* (%)	371 (42.8)	23 (42.6)	1	132 (53)	3 (23.1)	0.046	270 (44.9)	15 (35.7)	0.265
Cardiovascular disease, *n* (%)	60 (6.9)	7 (13)	0.104	23 (9.2)	3 (23.1)	0.127	52 (8.7)	6 (14.3)	0.257
Cancer, *n* (%)	29 (3.3)	3 (5.6)	0.428	11 (4.4)	0 (0)	1	18 (3)	1 (2.4)	1
NSAIDs, *n* (%)	362 (41.8)	17 (31.5)	0.155	104 (41.8)	6 (46.2)	0.78	203 (33.8)	16 (38.1)	0.614
Anticoagulant or antiplatelet agent, *n* (%)	362 (41.8)	17 (31.5)	0.155	104 (41.8)	6 (46.2)	0.78	203 (33.8)	16 (38.1)	0.614
Antipsychotic agent, *n* (%)	11 (1.3)	0 (0)	1	12 (4.8)	0 (0)	1	35 (5.8)	1 (2.4)	0.503
Hormone therapy, *n* (%)	43 (5)	1 (1.9)	0.509	8 (3.2)	0 (0)	1	12 (2)	1 (2.4)	0.588
Antihypertensive or blood pressure, *n* (%)	400 (46.1)	27 (50)	0.673	141 (56.6)	7 (53.8)	1	297 (49.4)	20 (47.6)	0.874
Diabetes medication, *n* (%)	62 (7.2)	3 (5.6)	1	37 (14.9)	1 (7.7)	0.699	49 (8.2)	5 (11.9)	0.385
Lipid-lowering medication, *n* (%)	342 (39.4)	24 (44.4)	0.477	113 (45.4)	7 (53.8)	0.58	267 (44.4)	21 (50)	0.523
Antidepressant, *n* (%)	203 (23.4)	18 (33.3)	0.102	96 (38.6)	7 (53.8)	0.383	245 (40.8)	20 (47.6)	0.419

Abbreviations: DE, dementia; MCI, mild cognitive impairment; NC, normal cognition.

TABLE 2 Covariate-adjusted effect of (top) LA/CA and (bottom) non-LA/CA treatments on AD biomarkers. LME coefficients, 95% confidence intervals, and *p*-values fitted to measured levels of Aβ42, t-tau, and p-tau in the CSF of participants with NC, MCI, and DE.

		NC				MCI				DE			
Biomarker	**EFFECT**	***β***	**Lower**	**Upper**	***p*-value**	***β***	**Lower**	**Upper**	***p*-value**	***β***	**Lower**	**Upper**	***p*-value**
Levodopa/carbidopa (LA/CA)													
Aβ42	INTERCEPT	527.3	350.9	703.6	<0.0001	188.8	−73.5	451.0	0.1579	315.1	163.3	466.9	0.0001
	TREATMENT	−361.6	−457.1	−266.2	<0.0001	−136.1	−236.7	−35.5	0.0081	−192.9	−276.6	−109.3	<0.0001
	AGE	1.2	−1.0	3.5	0.2907	2.3	−1.0	5.7	0.1723	1.8	−0.1	3.8	0.0678
	SEX	32.1	−8.9	73.0	0.1245	48.1	−14.2	110.5	0.1295	−38.4	−74.8	−2.0	0.0388
	APOE ε4	−93.2	−114.5	−71.9	<0.0001	−83.6	−114.1	−53.1	<0.0001	−61.9	−80.8	−42.9	<0.0001
p-tau	INTERCEPT	9.5	−5.2	24.2	0.2063	0.1	−41.6	41.8	0.9968	71.1	40.5	101.6	<0.0001
	TREATMENT	−15.8	−23.7	−7.9	0.0001	−18.5	−34.2	−2.9	0.0204	−30.7	−47.5	−14.0	0.0003
	AGE	0.6	0.4	0.8	<0.0001	0.7	0.2	1.3	0.0081	−0.1	−0.5	0.3	0.6596
	SEX	−1.9	−5.3	1.6	0.2871	7.7	−2.1	17.6	0.1248	4.1	−3.2	11.5	0.2684
	APOE ε4	4.4	2.6	6.1	<0.0001	14.9	10.1	19.8	<0.0001	7.5	3.7	11.3	0.0001
t-tau	INTERCEPT	−51.5	−178.8	75.9	0.4281	−104.8	−397.2	187.6	0.4816	457.4	206.6	708.2	0.0004
	TREATMENT	−204.5	−273.5	−135.5	<0.0001	−250.7	−363.0	−138.5	<0.0001	−316.4	−454.6	−178.2	<0.0001
	AGE	5.1	3.4	6.7	<0.0001	6.5	2.7	10.2	0.0008	−0.5	−3.8	2.7	0.7372
	SEX	0.7	−28.8	30.3	0.9611	−13.2	−82.7	56.3	0.7083	8.8	−51.4	68.9	0.7754
	APOE ε4	26.0	10.6	41.4	0.0009	66.9	32.9	100.9	0.0001	38.1	6.8	69.5	0.0171

(Continues)

TABLE 2 (Continued)

		NC				MCI				DE			
Biomarker	**EFFECT**	**β**	**Lower**	**Upper**	***p*-value**	**β**	**Lower**	**Upper**	***p*-value**	**β**	**Lower**	**Upper**	***p*-value**
Other antiparkinsonians (non-LA/CA)													
Aβ42	INTERCEPT	509.7	323.6	695.8	<0.0001	6.4	−9.3	22.1	0.4251	−74.7	−210.7	61.2	0.2812
	TREATMENT	−43.8	−126.7	39.2	0.3011	1.5	−5.5	8.5	0.6776	−23.3	−84.1	37.5	0.4521
	AGE	1.6	−0.8	4.0	0.1868	0.6	0.4	0.8	<0.0001	5.4	3.7	7.2	<0.0001
	SEX	27.4	−15.2	69.9	0.2070	−1.8	−5.4	1.8	0.3253	0.1	−31.0	31.2	0.9951
	APOE ε4	−95.9	−117.9	−73.8	<0.0001	4.5	2.7	6.4	<0.0001	27.2	11.0	43.3	0.0010
p-tau	INTERCEPT	113.4	−166.6	393.3	0.4264	−4.2	−49.5	41.0	0.8540	−142.0	−460.1	176.1	0.3807
	TREATMENT	145.1	8.8	281.4	0.0370	−7.4	−29.3	14.5	0.5062	−125.7	−280.5	29.1	0.1112
	AGE	3.2	−0.4	6.7	0.0850	0.8	0.2	1.4	0.0083	7.0	2.9	11.1	0.0008
	SEX	53.8	−12.4	120.1	0.1109	8.0	−2.6	18.6	0.1391	−9.9	−85.2	65.3	0.7952
	APOE ε4	−86.8	−119.7	−53.8	<0.0001	16.2	10.9	21.5	<0.0001	74.6	37.2	112.0	0.0001
t-tau	INTERCEPT	290.1	130.6	449.6	0.0004	70.4	38.2	102.6	<0.0001	460.1	196.5	723.8	0.0006
	TREATMENT	69.6	−1.5	140.7	0.0550	−7.7	−22.0	6.6	0.2921	−93.7	−211.2	23.8	0.1177
	AGE	2.1	0.0	4.1	0.0493	−0.1	−0.5	0.4	0.7693	−0.6	−3.9	2.8	0.7488
	SEX	−36.8	−74.9	1.3	0.0581	3.7	−4.0	11.4	0.3490	11.8	−51.1	74.8	0.7126
	APOE ε4	−63.9	−83.8	−44.0	<0.0001	7.9	3.9	11.9	0.0001	38.9	6.0	71.8	0.0204

Abbreviations: DE, dementia; MCI, mild cognitive impairment; NC, normal cognition.

TABLE 3 Characteristics of participants exposed to LA/CA and controls in the analyses of cognitive decline and survival rates.

	NC			MCI			DE		
Variable	**Controls**	**Cases**	***p*-value**	**Controls**	**Cases**	***p*-value**	**Controls**	**Cases**	***p*-value**
Levodopa/carbidopa (LA/CA)									
n	274	274		320	320		646	646	
Female, *n* (%)	132 (48.2)	124 (45.3)	0.549	81 (25.3)	91 (28.4)	0.422	195 (30.2)	176 (27.2)	0.268
Age in years (SD)	71.6 (8.9)	70.5 (7.8)	0.135	72.3 (9.9)	70.8 (9.2)	0.038	73.5 (9.6)	72.2 (8.7)	0.012
Apoe ε4, *n* (%)	58 (21.2)	45 (16.4)	0.189	64 (20)	70 (21.9)	0.627	208 (32.2)	213 (33)	0.812
Education level in years (SD)	17.2 (9)	16.7 (5.6)	0.433	15.7 (5.6)	16.6 (8.6)	0.124	15.6 (9)	16.1 (7.4)	0.327
Race/White, *n* (%)	216 (78.8)	258 (94.2)	<0.001	274 (85.6)	300 (93.8)	0.001	553 (85.6)	597 (92.4)	<0.001
Race/Black or African American, *n* (%)	36 (13.1)	7 (2.6)	<0.001	27 (8.4)	12 (3.8)	0.020	37 (5.7)	24 (3.7)	0.115
Race/Other, *n* (%)	22 (8)	9 (3.3)	0.025	19 (5.9)	8 (2.5)	0.047	56 (8.7)	25 (3.9)	0.001
Hypertension, *n* (%)	128 (46.7)	114 (41.6)	0.263	168 (52.5)	127 (39.7)	0.001	338 (52.3)	320 (49.5)	0.344
Cardiovascular disease, *n* (%)	48 (17.5)	38 (13.9)	0.290	51 (15.9)	57 (17.8)	0.598	110 (17)	101 (15.6)	0.547
Cancer, *n* (%)	16 (5.8)	7 (2.6)	0.086	24 (7.5)	12 (3.8)	0.058	38 (5.9)	14 (2.2)	0.001
NSAIDs, *n* (%)	102 (37.2)	121 (44.2)	0.117	140 (43.8)	133 (41.6)	0.632	210 (32.5)	234 (36.2)	0.178
Anticoagulant or antiplatelet agent, *n* (%)	102 (37.2)	121 (44.2)	0.117	140 (43.8)	133 (41.6)	0.632	210 (32.5)	234 (36.2)	0.178
Antipsychotic agent, *n* (%)	4 (1.5)	7 (2.6)	0.545	6 (1.9)	9 (2.8)	0.603	54 (8.4)	68 (10.5)	0.216
Hormone therapy, *n* (%)	11 (4)	10 (3.6)	1	3 (0.9)	8 (2.5)	0.223	8 (1.2)	13 (2)	0.379
Antihypertensive or blood pressure, *n* (%)	143 (52.2)	156 (56.9)	0.303	189 (59.1)	166 (51.9)	0.08	332 (51.4)	328 (50.8)	0.867
Diabetes medication, *n* (%)	29 (10.6)	28 (10.2)	1	52 (16.3)	26 (8.1)	0.002	73 (11.3)	46 (7.1)	0.012
Lipid-lowering medication, *n* (%)	129 (47.1)	105 (38.3)	0.047	151 (47.2)	129 (40.3)	0.094	292 (45.2)	293 (45.4)	1
Antidepressant, *n* (%)	41 (15)	100 (36.5)	<0.001	87 (27.2)	137 (42.8)	<0.001	271 (42)	285 (44.1)	0.465

Abbreviations: DE, dementia; MCI, mild cognitive impairment; NC, normal cognition.

t-tau and p-tau levels; no evident effect is identified for the variable "sex" (Table 2, bottom). The percentages of subjects with reported parkinsonian symptoms in the non-LA/CA case/control groups were 3.7%/4.0% (NC), 30.8%/3.6% (MCI), and 12.2%/6.0% (DE).

3.2 | Association between use of LA/CA and cognitive decline

Whereas the observation of lower CSF Aβ42 levels suggests changes in the Aβ metabolism, the t-tau- and p-tau-lowering effects might implicate reduced neurodegeneration and, consequently, slower cognitive decline. To test this hypothesis, all cases with reported use of LA/CA were assessed – including those without CSF biomarker data available – and a population of controls (without reported use of LA/CA) was defined upon automatic 1:1 matching by age, sex, and APOE ε4 (Table 3). The Kaplan–Meier method was then used to determine the cumulative probabilities of cognitive decline from NC to MCI/DE (Figure 4A) or from MCI to DE (Figure 4B). According to the log-rank Mantel-Cox tests that were performed, LA/CA exposure did not change the cognitive decline in NC subjects but increased the probability of no cognitive decline in MCI subjects ($p = 0.03$; log-rank hazard ratio 1.321 [95% confidence interval 1.020 to 1.710]). The delayed progression to dementia is quantified by a median-based effect size of 2.1 years.

3.3 | Association between use of LA/CA and registered death rates

We further speculated that the beneficial effects of LA/CA could also affect life expectancy. Kaplan–Meier curves were generated using the dates of death reported during the observation period (2005 to 2024) for the same NC and MCI populations that were assessed for cognitive decline. An analogous procedure was adopted for subjects with baseline DE who were prescribed LA/CA (cases) and respective controls matched by age, sex, and APOE ε4 allele (Table 3). In all these analyses, the probability of survival to death events was never increased in LA/CA-exposed groups (Figure 5). Survival rates decreased in the NC subgroup (Figure 5A, $p = 0.002$; log-rank hazard ratio 0.50 [95% confidence interval 0.334 to 0.763]) and remained unaltered in the MCI (Figure 5B) and DE (Figure 5C) subgroups.

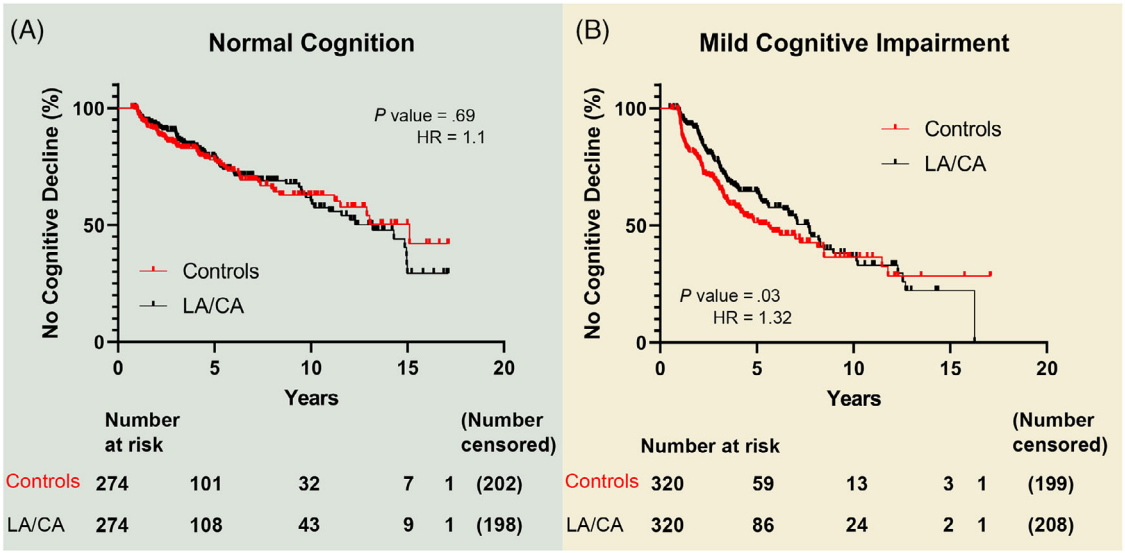

FIGURE 4 Resistance to cognitive decline by participants in LA/CA-exposed and LA/CA-naive samples. Kaplan–Meier analysis for events of cognitive decline by subjects with (A) NC and (B) MCI. *p*-values and hazard ratio (HR) values were obtained by the log-rank test. LA/CA, levodopa/carbidopa; MCI, mild cognitive impairment; NC, normal cognition.

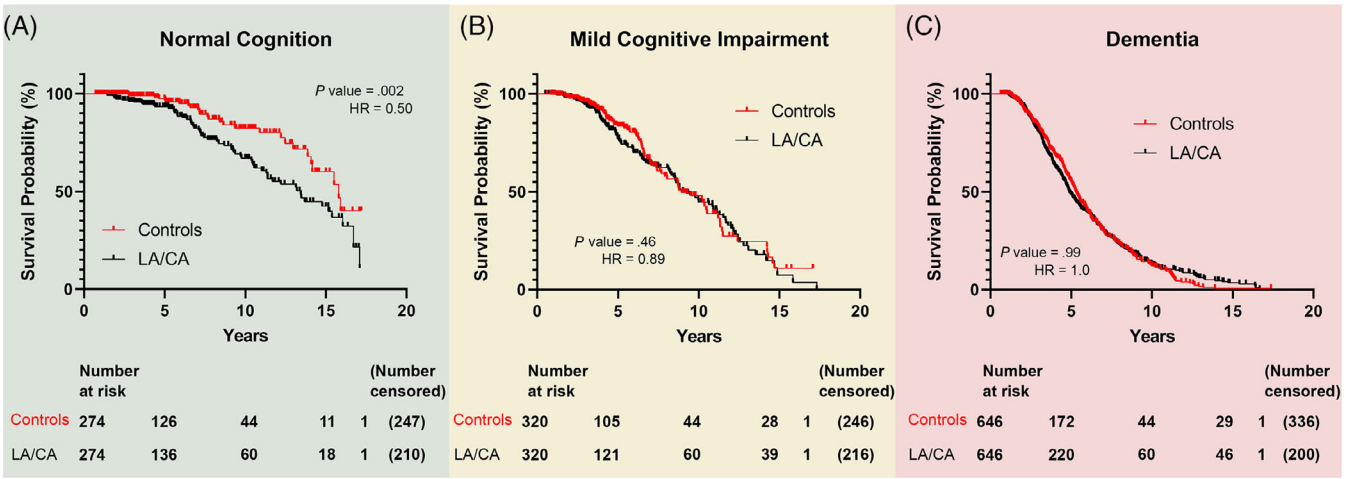

FIGURE 5 Overall survival of participants in LA/CA-exposed and LA/CA-naive samples. Kaplan–Meier analysis for death events by subjects with (A) NC, (B) MCI, and (C) DE. *p*-values and hazard ratio (HR) values were obtained by the log-rank test. DE, dementia; LA/CA, levodopa/carbidopa; MCI, mild cognitive impairment; NC, normal cognition.

4 | DISCUSSION

Our study retrospectively compared CSF biomarker levels, cognitive decline, and probability of death events among LA/CA-exposed and LA/CA-naive groups at different stages of cognitive impairment due to AD. Lower levels of CSF Aβ42, t-tau, and p-tau were consistently observed in LA/CA-exposed subjects diagnosed at baseline with NC, MCI, or DE. This association, which was adjusted for important covariates such as the presence of the APOE ε4 allele or age, was not verified for levodopa-sparing antiparkinsonians such as dopamine agonists. Remarkably, for MCI patients who showed both PD and AD symptoms, LA/CA exposure was additionally associated with a delayed progression to dementia of 2.1 years (median-based). This is a surprising result because, when AD pathology and Lewy body (LB) pathology (like PD and dementia with LB) are both exhibited, the cognitive decline is expected to be faster than when only AD or LB pathology is exhibited.[27,28] On the other hand, no effect of LA/CA use was observed on the probabilities of cognitive decline by NC subjects. Survival analysis of registered death events indicated no effect of LA/CA exposure in the MCI and DE subgroups and increased death rates in the NC subgroup.

Despite the limitations of using animal models to mimic AD in humans, previous results obtained with these models offer plausible explanations for the possible effects of LA/CA on AD progression.

Using a transgenic mouse model, Ambrée et al. showed that levodopa treatment ameliorated learning and memory deficits, increased the dopamine levels in the neostriata and frontal cortices, and decreased the dopamine levels in the hippocampus.[9] Later on, Guzmán-Ramos et al. observed that memory impairment was also attenuated after restoration of dopamine release deficits through retrodialysis administration of nomifensine.[10] It was argued that the increased availability of dopamine in specific regions of the brain might restore the dopaminergic equilibrium and working memory impairment and contribute to correcting the pronounced acetylcholine dysfunction characteristic of AD.[9,10] Subchronic treatment with levodopa of transgenic mice showing a selective vulnerability of dopaminergic neurons in the ventral tegmental area (VTA) completely rescued CA1 synaptic plasticity and dendritic spine density and restored hippocampal postsynaptic density composition, memory performance, and food reward processing.[6] Moreover, levodopa, as well as the dopamine D2 receptor agonists quinpirole and sumanirole, were able to ameliorate hippocampal hyperexcitability caused by the degeneration of dopaminergic VTA neurons.[8]

A disease-modifying effect of LA/CA might also be linked with the main histopathological hallmarks of AD, specifically the extracellular accumulation of the Aβ peptide in amyloid plaques and the intracellular deposition of protein tau. It was recently shown in vivo that levodopa promoted the degradation of Aβ in a neprilysin-dependent manner[29,30] and improved cognitive function,[30] but it did not affect tau pathology in 5xFAD mice.[29] Lower levels of CSF Aβ42 in LA/CA-exposed subjects could alternatively be explained by an increased accumulation of amyloid plaques.[23] Although Aβ aggregation is inhibited by dopamine,[31] metabolites arising from dopamine oxidation can stabilize Aβ oligomers and thus remodel the amyloid cascade of events.[32] Moreover, abnormal metabolism of Aβ42 may be a common feature of PD patients with MCI or DE.[33] Our observations of reduced levels of Aβ42, t-tau, and p-tau associated with exposure to LA/CA but not dopamine agonists shed some light on the potential use of CSF biomarkers in PD diagnosis. Although there is no consensus on how these biomarkers correlate with PD in studies not controlled for antiparkinsonian use,[33–37] reduced levels of the Aβ peptide and tau proteins are confirmed in a cohort of entirely untreated PD patients compared to healthy controls.[35] Furthermore, our multivariate analysis underlines the importance of the APOE ε4 genotypes in reducing Aβ42 levels and increasing t-tau and p-tau levels.

Intriguingly, the pronounced differences between CSF biomarker levels in the LA/CA groups and controls were never observed for the groups of other antiparkinsonian drugs and controls (Figure 3, and Table 2). Since the brain levels of dopamine are substantially increased by LA/CA but not by dopamine agonists,[38,39] the reduced levels of CSF Aβ42, t-tau, and p-tau are likely caused by dopamine-specific effects and not by the activation of presynaptic receptors. Identified using mouse models of AD,[29,30] the levodopa-induced upregulation of the neprylisin-mediated Aβ degradation may also account for altered CSF Aβ42 levels in AD patients given that CSF neprilysin activity was found to correlate negatively with CSF Aβ42.[40] In those patients, however, lower levels of CSF Aβ42 were associated with higher levels of CSF tau (and more neuronal damage), the opposite correlation we observed for the LA/CA groups (Figure 3, top). As previously suggested for spinocerebellar ataxia type 3 (SCA3, or Machado-Joseph disease), levodopa may contribute to less neuronal damage through a dopamine-mediated mechanism that prevents neurotoxic protein aggregation.[39,41] By counteracting dopaminergic depletion in the ventral striatum, levodopa may reduce Aβ deposition and widespread cognitive dysfunction.[42] Contrastingly, by selectively activating dopamine D1/D5 receptors,[43] dopamine agonists may contribute to restoring the impaired cortical plasticity,[44] as confirmed in transgenic mouse models of AD and WT mice administered with exogenous Aβ42 oligomers.[45] Based on the Human Protein Atlas for neurotransmitter receptor distribution,[46] CSF amyloid pathology is associated with brain volume atrophy in areas of high dopamine receptor densities, whereas CSF tau pathology is associated with less atrophy in areas of low dopamine receptor densities; these data suggest the existence of complex compensatory mechanisms across AD progression.[46]

We showed that LA/CA treatments were associated with reduced levels of biomarkers for Aβ42 metabolism and tau pathology. This relationship is not observed for levodopa-sparing antiparkinsonians and goes along with a significant delay in the progression to dementia of MCI patients, especially during the initial 6 to 7 years of follow-up (Figure 4B). There are similarities between the present results and our recent analysis of the natural history of patients diagnosed with SCA3: LA/CA but not other antiparkinsonian drugs were associated with delayed SCA3 progression at 6 years and (to a lesser extent) 13 years of disease monitoring, in an effect that was adjusted for age and genetic burden and that is possibly related to dopamine-mediated remodeling of protein aggregation pathways.[39] It has been reported that adverse effects associated with long-term use of levodopa start to manifest in PD 6 to 7 years after the onset of Parkinson's symptoms.[47] However, because motor complications can develop as early as 0.5 to 2 years after starting chronic use of levodopa, it is recommended that the lowest doses providing satisfactory clinical control be adopted.[48] Therefore, LA/CA treatments may benefit SCA3 and AD patients already showing aggravating signs of the disease, in line with the apparent delay in cognitive decline achieved for MCI subjects.

Levodopa doses typically start at 300 mg/day during early-stage PD and then increase to over 800 mg/day during advanced PD; doses below 300 mg/day are prescribed for the treatments of, for example, dopamine-responsive dystonia and restless leg syndrome.[49,50] Because >75 mg/day carbidopa is required to fully inhibit the peripheral AADC enzyme in adults,[51] LA:CA ratios of 4:1 and 10:1 are commonly used in commercial formulations designed for lifelong PD management. Even if parkinsonian symptoms are not manifested by most SCA3 or AD patients, the dopaminergic system is known to be affected in both diseases.[4–7,52,53] Thus, levodopa-based drugs with doses and LA:CA ratios adjusted to treat mild dopamine deficiency are conceived as possible approaches to delaying the progress of SCA3 and AD in the future.

The caveats of the present study are connected to its observational, retrospective, and exploratory nature, which greatly limits the ability

to infer causality between LA/CA and AD outcomes. Additional limitations arise from the poor control of drug dosing and adherence, comorbidities, concomitant medication, and demographic variables. Underreporting of treatments and/or mortality is an inherent risk arising from the self-reporting of medication use and the contingency that NACC is not always made aware of deaths for active and inactive subjects.[15,25,54] In this respect, because LA/CA medication is prescribed by healthcare professionals, the unreported use risks are lower than with over-the-counter medication. In our survival analyses, the populations are matched by sample size, initial diagnosis, age, sex, and presence of the APOE ε4 allele. This procedure promotes an even distribution of unreported death events between cases and controls. While the present study does not account for the risks of polypharmacy, no significant differences in cognitive decline were previously identified between groups exposed to 0 to 4, 5 to 9, and $\geq$10 medications.[55] Since the primary focus of the NACC-UDS is AD,[26] parkinsonian symptoms might be underreported for subjects exposed to dopaminergic drugs and controls. This is an important confounder given the faster cognitive decline expected when AD and LB pathologies are both exhibited.[27,28] Another limitation was the lack of drug exposure data prior to entry into the NACC-UDS database or close to the dates of CSF biomarker analysis. The latter uncertainty is mitigated through the exclusion of biomarker data obtained more than 2 years after the reports of prescribed medication. Since LA/CA exposure was dichotomized between users and non-users, no insights could be provided into the effect of dosing on the disease outcomes. The fact that patients prescribed levodopa alone or with adjunctive therapies such as carbidopa, entacapone, or dopamine agonists are all classified as LA/CA users further limits any inference about the best LA/CA strategies to be adopted in the future. As signaled in previous retrospective studies,[20] the nature of the NACC cohort and possible selection bias toward highly educated White participants may limit the general applicability of our findings. Therefore, the causal relationships hereby suggested between LA/CA use and disease outcomes require better-controlled clinical studies to be conclusively demonstrated toward the goal of effective and safe therapies for AD.

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CONFLICT OF INTEREST STATEMENT

The authors declare the following competing interests: Z.S., S.M.R., and P.M.M. are co-inventors in provisional patent applications for the use of low-dose levodopa formulations for the treatment of neurodegenerative disorders. J.D. served as a consultant for Biogen and Biohaven. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Each Alzheimer's Disease Research Center that contributes to the National Alzheimer's Coordinating Center Data Set is approved by their local institutional review board, and each collects written informed consent from all participants and co-participants.

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