Brain atrophy trajectories predict differential functional performance in Alzheimer’s disease: Moderations with apolipoprotein E and sex

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1 | BACKGROUND

Functional decline is a key characteristic of dementia including Alzheimer’s disease (AD).¹ Progressive functional decline in AD leads to increased caregiver burden² and loss of independence.³ Changes in complex activities such as financial planning and housework are commonly observed, followed by deficits in self-care activities. Instrumental activities of daily living (IADLs) are currently used to measure deficits in complex tasks in dementia.⁴ Previous reports show a positive correlation between caregiver and patient reports on everyday cognitive decline,⁵ and caregiver descriptions were more accurate for basic activities of daily living (ADLs) as cognition declined in older adults.⁶ A recent study suggested that identifying adults with functional difficulties may serve as an informal screening tool for older adults with high...
dementia risk profiles,7 who may benefit from a personalized medicine approach and intervention programs.

Functional decline is accelerated in AD compared to prodromal stages of dementia (ie, mild cognitive impairment [MCI]),8 and has been linked with several risk factors9 including cognitive impairment,10 brain atrophy,11 increased white-matter hyperintensity,12 genetics,13 sex,14 and dementia status.15 A multimodal risk approach integrating multiple domains16,17 with modifiable and non-modifiable risk factors is currently pursued in the field to predict accelerated cognitive trajectories in older adults18 and dementia patients.16 We apply a similar multimodal approach and extend previous work on cognitive changes to study differential functional trajectories in AD as predicted by three important and commonly studied risk domains (brain morphometry, genetics, and sex). Specifically, we examine whether brain atrophy (represented with brain parenchymal fraction [BPF]), key AD genetic risk marker (apolipoprotein E [APOE]), and sex in combination magnify functional decline (using IADL as a proxy) in AD.

Brain atrophy, especially loss of brain parenchyma as a result of neurodegeneration, is a key feature in AD.19 We use BPF to represent global brain atrophy.20 Previous reports show whole brain volume measures of cerebroal atrophy as a reliable source for measuring cognitive function,21 and positive correlation for total brain volume trajectory with age and diagnosis of mild cognitive impairment (MCI).22 The use of BPF is an intentional variable in our study, in that we sought to represent the overall brain atrophy trajectories in diagnosed AD cases commonly observed in real-world clinical settings.

The APOE genetic polymorphism (chromosome 19q13.2) has been identified consistently and established as the strongest genetic risk factor for cognitive impairment23 and functional decline.24 APOE has three isoforms (ε2, ε3, and ε4); where the ε4 is considered to have the highest risk for AD and cognitive impairment, ε3 as neutral, and ε2 as protective.23,25 APOE regulates lipid homeostasis and cholesterol metabolism important for amyloid beta (Aβ) aggregation and metabolism leading to plaques and cerebral amyloid angiopathy in AD.23,25 Previous work has shown that MCI adults with APOE ε4 allelic risk and higher brain atrophy may be at greater risk of functional decline.11 Inconsistent findings have also been reported for APOE ε4 risk and functional decline. Specifically, APOE ε4/ε4 homozygotes showed a slower rate of cognitive and functional decline compared to their counterparts (APOE ε4+ and APOE ε4− groups). This finding implies potential underlying differences between rates of decline in the APOE ε4 homozygous group versus early diagnosis observed in APOE ε4 carriers alone.26

Sex differences in AD showed that women with cognitive impairment (ie, executive function) had worse basic ADLs and IADLs over 6 years and increased mortality risk.14 In addition, women with lower performance on IADLs were observed to be frailer with poor cognitive performance and greater falls.27 APOE ε4 carriers also showed increased loss of cortical thickness and hippocampal volume linked to accelerated cognitive decline,23 and functional impairment selectively in women.13

To our knowledge this is the first study to examine whether the synergistic associations of brain atrophy, APOE, and sex influence functional performance and decline in AD. We test atrophy and functional associations as moderated by three separate risk moderations (1) APOE, (2) sex, and (3) high-risk group (women APOE ε4 carriers). For our foundational analyses, we examine (1) 2-year individual trajectories of global atrophy and (2) a latent growth model of functional performance and decline. We expect to observe two classes of atrophy trajectories corresponding to low and high atrophy progression and a random intercept and slope growth model for functional decline. We examine three sequential research goals (RGs).

RG1: We examine whether atrophy classes predict functional performance and decline. We expect to observe that higher atrophy class predicts poorer functional performance and steeper decline.
TABLE 1  Baseline characteristics of AD patients in the Sunnybrook Dementia Study and Alzheimer’s Disease Neuroimaging Initiative by apolipoprotein E (APOE) ε4 status

| Characteristics | APOE ε4− (SDS) | APOE ε4− (ADNI) | APOE ε4+ (SDS) | APOE ε4+ (ADNI) | Total (SDS) | Total (ADNI) |
|----------------|----------------|----------------|----------------|----------------|------------|-------------|
| n              | 61             | 61             | 109            | 123            | 170        | 184         |
| Age (years)    | 72.6 (9.8)     | 76.4 (8.5)     | 70.6 (8.7)     | 74.4 (6.9)     | 71.3 (9.1) | 75.1 (7.5)  |
| Sex (M/F)      | 35/26          | 26/35          | 42/67          | 69/54          | 77/93      | 95/89       |
| Education (years) | 14.1 (4.1)   | 15.0 (3.4)     | 13.8 (3.8)     | 14.5 (3.1)     | 13.9 (3.9) | 14.7 (3.2)  |
| MMSE           | 24.2 (3.3)     | 23.3 (2.0)     | 24.0 (3.3)     | 23.3 (2.0)     | 24.1 (3.3) | 23.3 (2.0)  |
| BPF (%)        | 73.3 (4.2)     | 65.9 (3.1)     | 74.3 (4.8)     | 66.1 (2.3)     | 73.9 (4.6) | 66.0 (2.6)  |
| BPF (%) range  | 62.23-80.83    | 59.84-74.00    | 63.26-86.37    | 60.35-72.87    | 62.23-86.37 | 59.84-74.00 |
| IADL-DAD (%)   | 76.3 (21.6)    | –              | 75.6 (23.7)    | –              | 75.8 (22.9) | –           |
| IADL-DAD range | 30-100         | –              | 7-100          | –              | 7-100      | –           |
| FAQ range      | –              | 1.30           | –              | 0.29           | –          | 0.30        |

Note. Means are represented with standard deviations in parentheses. Abbreviations: ADNI, Alzheimer’s Disease Neuroimaging Initiative; APOE, apolipoprotein E; BPF, brain parenchymal fraction; FAQ, Functional Activities Questionnaire; IADL-DAD, Instrumental Activities of Daily Living-Disability Assessment Scale; MMSE, Mini-Mental State Exam; n, sample size; SDS, Sunnybrook Dementia Study.

RG2: We test whether the observed association between atrophy class and functional performance and decline is moderated by APOE (ε4− vs ε4+) and sex (men vs women), independently. We expect that higher atrophy class will predict poorer functional performance and steeper decline in APOE ε4+ carriers and women, separately.

RG3: We examine whether the observed atrophy class and functional performance and decline association is moderated by high APOE and sex risk combination (women APOE ε4 carriers) versus the low-risk group (women in the APOE ε4− group and men in the APOE ε4− and ε4+ groups). We expect to observe worse functional performance and steeper decline in high-risk group with higher atrophy class.

We aim to validate all our findings using the Alzheimer’s Disease Neuroimaging Initiative (ADNI) as a replication sample.

2  METHOD

2.1  Participants

2.1.1  Sunnybrook Dementia Study (SDS)

We used data from the SDS (ClinicalTrials.gov NCT01800214), a large longitudinal observational prospective cohort study (1994 to the present) of dementia patients in Toronto, Canada. The SDS includes clinical data, standardized neuroimaging, neuropsychology, function, mood, behavior, and genetic assessments. All patients were recruited from the Sunnybrook Health Sciences Centre Cognitive Neurology Clinic, University of Toronto, Canada. All patients were enrolled through physician referrals to a tertiary memory clinic and older adults through word of mouth or advertisements. Institutional human research ethics guidelines were met in full for ongoing data collection procedures. Written informed consent was obtained from all participants. If participants were deemed too demented, their power of attorney provided consent on their behalf. For the present study, we included diagnosed AD patients tested across three waves (~2 years). AD was diagnosed using the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer’s disease and Related Disorders Association criteria. Mini-Mental State Exam (MMSE) score of 16 is shown to be a key transition point for loss of IADLs; thus in the present study, we excluded patients with MMSE below 16 (n = 11) and those with missing APOE genotype data or unusable baseline magnetic resonance imaging (MRI) scans. Accordingly, 170 AD patients (age range = 46 to 89 years; mean age = 71.3 (9.1) years; n women = 93) were included (Table 1).

2.1.2  ADNI (replication sample)

Data used in our replication sample were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. We included 184 AD patients (mean age = 75.1 (7.5) years; n women = 89) from ADNI-1. Specifically, only AD patients with both clinical data in the “ADNIMERGE” table and imaging data from “UCSDVOL” table downloaded on March 26, 2020, were included. The selected patients were similar in severity and age of AD patients in the SDS (see Table 1). We included longitudinal structural imaging data from the “UCSDVOL” table across three time points (baseline, Years 1 and 2) and baseline data from “ADNIMERGE” table.
2.2 MRI acquisition protocols and processing

2.2.1 SDS

Structural brain images were obtained on a 1.5T GE Signa (Milwaukee, WI, USA) system. We examined global brain atrophy with the BPF measure using normal-appearing gray matter (NAGM), normal-appearing white matter (NAWM), and white matter hyperintensities (WMHs). Specifically, BPF = (NAGM + NAWM + WMH/(supratentorial total intracranial volume [ST-TIV]) x 100. Higher BPF corresponds to lower atrophy. Brain volumetrics were estimated from structural MRI using a previously published and validated segmentation algorithm.\textsuperscript{32–35}

2.2.2 ADNI (replication sample)

MRI data image acquisition and processing have previously been described.\textsuperscript{31,36} To calculate BPF, we used BPF = (Whole brain volume/total intracranial volume [TIV]) x 100 from the "UCSDVOL" table. Higher BPF volume corresponds to lower atrophy. We note that the BPF in ADNI uses the supra- and infratentorial intracranial volume as denominator, whereas SDS uses only the supratentorial intracranial compartment. Although there are differences between the SDS and ADNI in calculating BPF, the analyses for each study were conducted independently; the larger denominator (TIV includes infratentorial volumes) in the ADNI sample should not exert any variance relative to the smaller denominator (ST-TIV includes only supratentorial volume) in the SDS sample.

2.3 Genotyping

APOE \( \varepsilon 4 \) genotyping was performed using DNA extraction in both the SDS\textsuperscript{37} and ADNI.\textsuperscript{38} All \( \varepsilon 2/\varepsilon 4 \) cases were excluded because of conflicting reports on \( \varepsilon 2 \) protective effects versus \( \varepsilon 4 \) risk associations.\textsuperscript{39} APOE genotype frequencies did not deviate from Hardy-Weinberg equilibrium in the SDS or ADNI.

2.4 Functional activities of daily living

2.4.1 SDS

We examined IADLs from the Disability Assessment for Dementia (DAD).\textsuperscript{4} Patients’ caregivers are asked whether the patient performed certain activities to maintain an adequate lifestyle in the last 2 weeks. For example, “adequately plan a light meal or snack” or “show an interest in leisure activities” with a no (0) or yes (1) for each of initiation, planning, and action sections on the DAD form. From 46 total items, 27 items on the second half of the form measure instrumental activities. Specifically, 8 items for initiation, 6 items for planning, and 13 items for action. The total score was calculated using the 27 IADL items as a percentage of 100,\textsuperscript{40} with higher scores representing greater functional activities.

2.4.2 ADNI (replication sample)

We used the Functional Activities Questionnaire (FAQ),\textsuperscript{41,42} which measures IADLs (eg, preparing meals). The FAQ is ideal for following rate of functional impairment over time in clinical patients. The scores range from dependent (3) to normal (0) for a total score out of 30, with higher scores indicating greater impairment.

2.5 Statistical analyses

Descriptive statistics were calculated for all baseline characteristics in the SDS and ADNI. Continuous measures such as age were summarized using means and standard deviations, whereas categorical measures were summarized using counts and percentages. We used structural equation modeling in Mplus 7.4\textsuperscript{43} to examine BPF latent growth model and class trajectories, latent growth model for functional activities, and the three RGs in the SDS and ADNI. Baseline age and education were added as covariates in all three RG analyses.

2.5.1 BPF latent growth model and class trajectories

First, we estimated the best latent growth model for BPF over 2 years using latent growth modeling. Second, we classified BPF into distinct groups by performing latent class growth analysis (LCGA). LCGA uses individual levels and slopes to calculate distinct classes (see Supplementary text).

2.5.2 Latent growth model for functional activities

We estimated the best latent growth model for functional activities (SDS: IADL-DAD; ADNI: FAQ) over 2 years using latent growth modeling (see Supplementary text).

2.5.3 RG1: Brain atrophy classes predicting functional decline

We regressed functional activities (intercept) and 2-year change (slope) on atrophy class.

2.5.4 RG2 and RG3: Moderation analysis with APOE \( \varepsilon 4+ \), sex, and high-risk group

Path analysis for functional activities on atrophy class (RG1) was repeated as stratified by (1) APOE \( \varepsilon 4-/\varepsilon 4+ \), (2) sex (men/women), and (3) high-risk group (women APOE \( \varepsilon 4 \) carriers/women in the APOE \( \varepsilon 4- \) group and men in the APOE \( \varepsilon 4- \) and \( \varepsilon 4+ \) groups). Moderation effect was calculated using the \( D \) statistic between the unconstrained and
TABLE 2  Goodness of fit indexes for one-to-three class brain parenchymal fraction latent growth class models in the Sunnybrook Dementia Study (SDS) and the Alzheimer’s Disease Neuroimaging Initiative (ADNI)

| Model | Class | AIC   | BIC   | −2LL | Entropy | Probability | Proportion | n  |
|-------|-------|-------|-------|------|---------|-------------|------------|----|
| SDS:  | 1     | 1     | 1847.668 | 1863.347 | 1837.668   | 1.000       | 1.000      | 170 |
|       | 2     | 1     | 1728.791 | 1753.877 | 1712.790   | 0.738       | 0.914      | 75  |
|       | 3α    | 1     | 1689.287 | 1723.781 | 1667.286   | 0.741       | 0.905      | 67  |
| ADNI: | 1     | 1     | 1958.626 | 1974.700 | 1948.626   | 1.000       | 1.000      | 184 |
|       | 2     | 1     | 1791.203 | 1816.923 | 1775.204   | 0.770       | 0.939      | 120 |
|       | 3α    | 1     | 1676.049 | 1711.413 | 1654.048   | 0.842       | 0.871      | 23  |
|       | 2     | –     | –       | –      | –         | 0.919       | 0.333      | 64  |
|       | 3α    | –     | –       | –      | –         | 0.944       | 0.495      | 94  |

Note. aBest fitting model.
Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; −2LL, −2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimated model; n, sample size.

3 | RESULTS

Our sample included 170 AD patients (age range = 46 to 89 years; mean age = 71.3 (9.1) years; n women = 93) in the SDS and 184 AD patients (age range = 55 to 91 years; mean age = 75.1 (7.5) years; n women = 89) in ADNI (replication sample) (Table 1). Standardized β coefficients are reported.

3.1 | BPF growth model and class trajectories

The best latent growth model was obtained with random intercept and random slope model and the 3-class LCGA model showed the best fit for BPF (see Table 2). We replicated these results in ADNI (see Table 2). Figure 1 shows the trajectories for BPF and the three distinct classes as represented by LCGA. In order of decreasing BPF, we define the classes as low (highest BPF), intermediate, and high global atrophy over 2 years.

3.2 | Latent growth model for functional activities

The random intercept and random slope latent growth model provided the best fit for functional activities (see Table 3) in the SDS and ADNI.

3.3 | RG1: Brain atrophy classes predict functional decline

Higher atrophy class was associated with lower functional performance (intercept; β = −0.263, SE = 0.083, P = .002) and steeper decline (slope; β = −0.351, SE = 0.118, P = .003) in the SDS. Higher atrophy class was associated with lower functional performance (β = 0.243, SE = 0.087, P = .005) in ADNI (see Figure 2A). We note that higher FAQ performance (in ADNI) represents lower functional performance.

3.4 | RG2: Moderations with APOE and sex

First, we observed that APOE moderated the association between atrophy class and functional performance (see Figure 2B). In the SDS, higher atrophy class was associated with lower functional performance (intercept; β = −0.299, SE = 0.102, P = .003) in the APOE ε4+ group. In ADNI, higher atrophy class was associated with lower functional performance (intercept; β = 0.286, SE = 0.101, P = .005) in the APOE ε4+ group and steeper decline (slope; β = 0.362, SE = 0.159, P = .023) in the APOE ε4− group.

Second, we observed that sex moderated the association between atrophy class and functional performance (see Figure 2C). In the SDS, higher atrophy class was associated with lower functional performance (intercept; β = −0.340, SE = 0.104, P = .001) and steeper decline (slope; β = −0.548, SE = 0.137, P < .001) for women. In ADNI, higher atrophy class was associated with steeper functional decline (slope; β = 0.331, SE = 0.129, P = .010) in men.
**Sunnybrook Dementia Study:**

![Graph showing brain atrophy trajectories over 2 years]

**FIGURE 1** Global brain atrophy trajectories over 2 years (represented with brain parenchymal fraction [%]) in the Sunnybrook Dementia Study and the Alzheimer’s Disease Neuroimaging Initiative. Three classes representing low (red), intermediate (blue), and high (green) atrophy were identified.

**TABLE 3** Latent growth model fit statistics and chi-square difference test for functional activities by wave in the Sunnybrook Dementia Study (SDS) and the Alzheimer’s Disease Neuroimaging Initiative (ADNI)

| Functional activities (SDS) | Model                         | H0 value   | Free parameters | −2LL   | AIC     | BIC     | D (dfD) |
|-----------------------------|-------------------------------|------------|----------------|--------|---------|---------|---------|
|                             | Fixed intercept               | −1207.452  | 4              | 2414.904 | 2422.905 | 2434.974 | –       |
|                             | Random intercept              | −1196.456  | 5              | 2392.912 | 2402.913 | 2417.999 | 21.992 (1)** |
|                             | Random intercept, fixed slope | −1171.758  | 6              | 2343.516 | 2355.516 | 2373.619 | 49.316 (1)** |
|                             | Random intercept, random slope| −1167.190  | 6              | 2334.380 | 2346.379 | 2364.483 | 9.136 (0.1)* |
|                             | Random intercept, random slope, fixed quadratic | −1166.535 | 7 | 2333.070 | 2347.071 | 2368.192 | 1.310 (1) |

| Functional activities (ADNI) | Model                         | H0 value   | Free parameters | −2LL   | AIC     | BIC     | D (dfD) |
|-------------------------------|-------------------------------|------------|----------------|--------|---------|---------|---------|
|                             | Fixed intercept               | −1643.806  | 4              | 3287.612 | 3295.613 | 3308.472 | –       |
|                             | Random intercept              | −1563.891  | 5              | 3127.782 | 3137.783 | 3153.857 | 159.830 (1)** |
|                             | Random intercept, fixed slope | −1484.460  | 6              | 2968.920 | 2980.921 | 3000.211 | 158.862 (1)** |
|                             | Random intercept, random slope| −1477.591  | 7              | 2955.182 | 2965.182 | 2991.686 | 13.738 (1)* |
|                             | Random intercept, random slope, fixed quadratic | −1474.203 | 8 | 2948.406 | 2964.405 | 2990.125 | 6.776 (1) |

Abbreviations: H0, Log Likelihood; −2LL, -2 Log Likelihood; AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; D, Deviance statistic; dfD, Degrees of freedom for difference in deviance statistics.

*a* = residuals for instrumental activities at a specific time point was constrained to zero for the model to work and difference of one was used to calculate the P-value.

*P < .05.

**P < .001.

### 3.5 RG3: Moderation with the high-risk group

We observed that the high-risk group moderated the association between atrophy class and functional performance and decline (see Figure 2D). In the SDS, higher atrophy class was associated with lower functional performance (intercept; \( \beta = -0.351, SE = 0.122, P = .004 \)) and steeper decline (slope; \( \beta = -0.515, SE = 0.164, P = .002 \)) in the high-risk group (women APOE ε4 carriers). In ADNI, higher atrophy
class was associated with lower functional performance (intercept: $\beta = 0.499, SE = 0.183, P = .006$) in the high-risk group and steeper functional decline (slope: $\beta = 0.309, SE = 0.107, P = .004$) in the low-risk group.

Significant moderations were observed with the $D$ statistics for all three moderations (see Tables S1 and S2).

4 | DISCUSSION

We observed that higher brain atrophy class predicted lower functional performance and steeper decline. This association was differentially moderated by $APOE$, sex, and high-risk combination (women $APOE\ e4$ carriers). Specifically, women $APOE\ e4$ carriers showed exac-
erbated baseline functional performance. Key novel contributions and findings of our study include: (1) latent classes analyses identifying distinct 2-year brain atrophy trajectories; (2) using brain atrophy classes to predict differential functional performance and decline in AD and as moderated with APOE, sex, and APOE and sex high-risk combination; and (3) replicating baseline functional impairment is magnified in women APOE ε4 carriers with higher brain atrophy class in a large independent AD cohort (ADNI).

For RG1, higher atrophy class predicted lower functional performance and steeper decline. We replicated our baseline findings in ADNI. Recent study showed that a combined score representing WMH, lacunes, gray matter, and hippocampal volume may be a stronger predictor of cognitive and functional activities in cerebral small vessel disease than specific brain regions. Our finding suggests that global brain atrophy patterns (using latent BPF classes) may identify distinct subgroups of AD patients at risk for accelerated functional impairment and those who may potentially benefit the most from personalized medicine (ie, tailored care and help to manage daily activities) and early intervention programs.

For RG2, APOE ε4 carriers with the higher brain atrophy class had lower functional performance. Previous studies have reported inconsistent results for APOE ε4+ and functional status in non-demented older adults and MCI participants. Our finding extends prior work by (1) confirming APOE ε4+ as a risk factor for functional impairment in a clinically diagnosed AD sample, and (2) replicating our findings in ADNI. As expected, higher global atrophy class and lower functional performance and steeper decline were observed selectively for women. Our results supplement previous work where women are observed to be at a higher risk overall. For example, women show (1) faster rates of atrophy, (2) steeper age-related decline in cognition, and (3) longer survival rates leading to higher percentage of AD dementia diagnosis.

For RG3, we observed that women APOE ε4 carriers had worse functional performance with higher atrophy class than their low-risk counterparts and this finding was replicated in ADNI. Previous work has shown that non-demented women APOE ε4 carriers show decreased connectivity in the anterior cingulate cortex compared to women APOE ε3 carriers and men ε4 carriers, and may have greater AD pathology, as detected at autopsy. In addition, men have higher levels of sterol regulatory element-binding protein (SREBP) 2 expression, where SREBP2 protein interacts with APOE to regulate lipid homeostasis possibly contributing to an overall lower risk for men. To our knowledge this is the first study to confirm APOE and sex magnification for differential functional performance using latent global brain atrophy classes in AD. Future work examining the complex interactions between global brain atrophy, APOE, and sex should consider including asymptomatic older adults and other neurodegenerative groups (ie, vascular dementia) to identify adults with potentially high functional dependence risk profiles.

We note several strengths and limitations of the present study. For limitations, first, we used BPF to represent global brain atrophy and past studies have focused on specific brain region such as hippocampal volume, WMH, and cortical atrophy to study functional impairment. Our aim was to focus on whether non-modifiable risk factors (APOE and sex) magnify the risk of global brain atrophy. Future work should consider examining specific AD regions (ie, hippocampal volume) to target areas with greater AD-related atrophy and to compare differences between specific brain regions associated with functional impairment. Second, we note several differences in findings between the SDS and ADNI replication sample: (1) in the SDS, higher brain atrophy class predicted steeper functional decline overall, in APOE ε4 carriers, women, and women APOE ε4 carriers but these associations were not observed in ADNI; (2) in ADNI, higher brain atrophy class predicted steeper functional decline in the APOE ε4– group, men, and low-risk group, but these associations were not present in the SDS. These variations may be due to measurement differences in IADL (DAD-IADL in SDS vs FAQ in ADNI), and other biomarkers and risk factors (ie, cerebrospinal fluid biomarkers) should be considered to elucidate this discrepancy. Future work with larger sample sizes and longer follow-up of AD patients should be examined to confirm our findings. Third, we note that data on racial backgrounds were not available in the SDS and our ADNI replication sample was predominately White, not of Hispanic origin (93.5%). Future work should consider replicating our findings using diverse racial backgrounds. Fourth, we focused on global atrophy in AD patients so we did not explore other non-AD pathologies (such as traumatic brain injury, stress and homocysteine levels contributing to neurodegeneration).

Among strengths, first, our diagnosed AD sample is representative of dementia patients in a real-world tertiary clinical setting. The SDS follows a research embedded in care approach and all recruited participants in our study are followed over time or as long as needed in our neurology clinic. Second, to our knowledge, this is first study to replicate such a complex magnification effect (brain atrophy, APOE, sex) associated with functional trajectories in AD. Third, we apply a novel approach by identifying distinct latent classes of brain atrophy trajectories and using this to predict functional performance and change.

In sum, distinct global brain atrophy patterns predicted functional trajectories in AD. Specifically, APOE ε4 carriers showed lower functional performance with higher brain atrophy class, and this association was magnified in women APOE ε4 carriers. Although women and APOE ε4+ risk are considered independent risk factors for functional decline, our findings suggest that the combined risk of women APOE ε4 carriers with global brain atrophy may be greater and highly influential than each risk domain separately. Such complex and dynamic multidomain interactions should be considered in intervention programs and clinical trial designs. Our study emphasizes the importance of applying a multidomain approach to identify patients with high functional dependence risk profiles who may benefit from early detection and personalized care.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE
All of this research has been approved continuously by relevant institutional review boards. Certificates are available from and on file at Sunnybrook Health Sciences Centre. All participants have completed and signed informed consent forms.

CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

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