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RESEARCH ARTICLE

Effects of exercise versus usual care on older adults with amnestic mild cognitive impairment: EXERT versus ADNI

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Abstract

INTRODUCTION: EXERT was a multisite randomized controlled trial (RCT) examining the effects of moderate-high intensity aerobic training (AX) versus lower-intensity stretching/balance/range of motion (SBR) on cognitive trajectories in older adults with amnestic mild cognitive impairment (aMCI).

METHODS: Preplanned post-hoc analyses were conducted to compare each arm to a propensity-matched usual care (no intervention) group from Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) selected for similarity across key characteristics. Differences in 12-month trajectories in the primary endpoint (ADAS-Cog-Exec) and magnetic resonance imaging (MRI) volumes in prespecified brain regions were compared.

RESULTS: AX and SBR showed significantly less 12-month cognitive decline than ADNI-1 (AX:n = 109, β = 0.169, 95% confidence interval [CI] 0.011–0.328; SBR:n = 105, β = 0.181, 95% CI 0.007–0.354). There were trends of less prefrontal cortex volume loss for both EXERT groups and less AD signature region volume loss for SBR relative to ADNI-1 over 12 months.

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DISCUSSION: Moderate-high intensity aerobic or low-intensity flexibility exercise for 12 months in participants with aMCI may provide protection against decline relative to usual care.

CLINICAL TRIAL REGISTRATION: The EXERT clinical trial is registered at clinicaltrials.gov (NCT02814526).

KEYWORDS
aging, clinical trial, cognition, cognitive function, exercise, mild cognitive impairment, older adults, physical activity, sedentary

Highlights

- EXERT was a randomized controlled trial in sedentary older adults with aMCI.
- EXERT arms were propensity-matched to a usual care (no intervention) group (Alzheimer's Disease Neuroimaging Initiative 1 [ADNI-1]).
- High and low-intensity exercise arms had less 12-mo cognitive decline than ADNI-1.
- There were trends of less prefrontal cortex volume loss for each arm versus ADNI-1.

1 | BACKGROUND

Estimates in 2017 reported that 2.43 million Americans had mild cognitive impairment (MCI) due to Alzheimer's disease (AD), and this number is expected to grow to 5.70 million by 2060.[1] Individuals with amnestic MCI (aMCI), which is characterized by memory complaints and objective memory decline, progress to AD dementia at a rate of 16% per year.[2] Thus, aMCI represents a critical stage for safe, accessible, and effective interventions to slow or reverse the trajectory of cognitive decline to prevent the occurrence of AD.

Exercise may be a potential intervention to prevent cognitive decline and dementia; however, evidence supporting an association between exercise and cognitive or other brain health outcomes has been mixed. Some prospective observational studies and meta-analyses have shown that greater physical activity in midlife or late life is associated with better cognitive performance, reduced risks of cognitive impairment and dementia, and increased hippocampal volume in older adults.[3–14] Other studies have shown no associations between physical activity and cognitive decline or dementia.[15–17] Exercise could positively impact cognitive and brain health via several mechanisms, including enhancing neural connectivity and increasing cerebral perfusion, synaptic plasticity, neurogenesis, and regulation of trophic factors.[18] Furthermore, there is some evidence from randomized controlled trials (RCTs) that regular exercise has cognitive benefits for older adults with MCI.[14,19–29] In a meta-analysis of 11 RCTs among 1497 older adults with MCI (62% female; mean age, 74.1 years), aerobic exercise led to significant improvements on tests of global cognitive function (i.e., Mini-Mental State Examination, Montreal Cognitive Assessment) and memory (i.e., immediate recall and delayed recall).[19] Other studies reported exercise benefits on executive function in those at increased risk for dementia.[30,31] These results remain tenuous, however, as trials of exercise in older adults with MCI generally had high potential for bias, significant heterogeneity of effects between studies, small sample sizes, and short intervention durations. Moreover, meta-analyses have also reported that other modes of exercise (e.g., strength training, yoga, Tai Chi) also have the potential to positively impact cognitive functioning in older adults.[32,33] To date, no large, multi-site study has been conducted to evaluate the potential therapeutic effects of aerobic exercise on brain health and markers of disease progression in older adults with aMCI.

The EXERT trial (Therapeutic Effects of Exercise in Adults with Amnestic Mild Cognitive Impairment) was designed to test whether 12 months of supervised moderate-high intensity aerobic training (AX) was more effective than lower intensity exercise involving stretching, balance, and range of motion (SBR) in improving or protecting cognitive function against decline in sedentary older adults with aMCI. The EXERT trial reported no difference in change on the ADAS-Cog-Exec (global cognitive composite score, primary outcome) after 12 months of low intensity or moderate-high intensity physical exercise intervention (Baker et al., in press). However, the EXERT trial design did not include an untreated "usual care" arm. This decision was based on (1) pre-study feedback from community focus groups about the importance of offering participants assignment to one of two exercise groups rather than possibly to a usual care group; (2) a study design decision to distinguish intervention groups by exercise mode and intensity with amount of social contact kept constant; (3) budgetary constraints that could accommodate only the two intervention groups; and (4) an ethical obligation to provide active comparison groups due to well-accepted exercise-related health benefits. Therefore, we developed a preplanned post-hoc investigation to compare the cognitive trajectories of the EXERT moderate-high and low-intensity exercise interventions to those of "usual care" using a matched sample of participants with aMCI enrolled in the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) observational study. ADNI-1 was selected as an ideal usual care comparison cohort for EXERT interventions given the studies' similarities in participant characteristics

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and cognitive tests administered.[34] In the present investigation, we compared 12-month trajectories of the EXERT primary cognitive outcome (ADAS-Cog-Exec)[35] and brain volumetric MRI outcomes for each intervention group (AX, SBR) versus propensity-matched ADNI-1 participants with aMCI.

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed using PubMed and MEDLINE. There is some evidence from randomized controlled trials (RCTs) that regular exercise has cognitive benefits for older adults with amnestic mild cognitive impairment (aMCI). However, these results remain tenuous, as trials of exercise in older adults with aMCI generally had small sample sizes and short intervention durations.
2. **Interpretation**: Sedentary older adults with aMCI in the aerobic exercise and stretching/balance/range of motion arms from the EXERT trial showed significantly less decline on a global cognitive composite score during the 12-month intervention than did similar adults with aMCI over a 12-month period in a large "usual care" observational study (Alzheimer's Disease Neuroimaging Initiative 1 [ADNI-1]).
3. **Future directions**: The potential protective effect of trainer supported low-intensity as well as moderate-high intensity exercise relative to usual care increases the feasibility and probability of the adoption of an exercise intervention in the wider community of older adults.

2 | METHODS

2.1 | EXERT study design overview

EXERT was a multisite, randomized controlled study examining the effects of moderate-high intensity (aerobic) exercise versus low intensity stretching, balance, and range of motion exercise on cognitive trajectory in a planned sample of 300 sedentary older adults with aMCI (clinicaltrials.gov: NCT02814526). EXERT partnered with the YMCA of the USA (Y-USA) to implement the interventions in community YMCA branches to enhance the external validity and translatability of the design. Participants were randomized to the AX or SBR group and completed their assigned interventions at a local YMCA with trainer supervision for 12 months and without supervision (independently) for an additional 6 months at the YMCA. Centralized training, intervention oversight, and regular site visits supported intervention delivery fidelity. Outcomes assessments were completed at baseline (pre-randomization) and at months 6, 12, and 18, with the primary endpoint pre-specified at month 12 at the end of the supervised phase of the intervention. The primary outcome was change on the ADAS-Cog-Exec, a validated composite measure of global cognitive function that supplements the ADAS-Cog13 with tests of executive function (see Section 2.6 for further details).[35] The Alzheimer's Disease Cooperative Study (ADCS) at the University of California San Diego coordinated the trial, in partnership with Wake Forest University School of Medicine and the Y-USA for intervention delivery oversight. EXERT recruitment strategies are published.[36] The study was conducted in accordance with The Code of Ethics of the World Medical Association and was approved by the Institutional Review Boards of the University of California San Diego, Wake Forest University School of Medicine, and each participating clinical site.

2.2 | EXERT participants

The target for EXERT enrollment was 300 sedentary older adults 65–89 years with aMCI at 13 clinical sites across the US. Sedentary status was assessed during an initial screening visit (typically by telephone) using a modified Telephone Assessment of Physical Activity (TAPA) questionnaire[37] to identify adults who were not already regular exercisers and thus largely sedentary. Light physical activity (e.g., leisure walking, light house or yard work) and low volume but more strenuous activity (e.g., < 20 min/day for no more than 2 days/week) were not exclusionary. Amnestic MCI was identified by a global Clinical Dementia Rating (CDR) of 0.05 with a memory box score of ≥0.5,[38] Mini-Mental State Exam (MMSE) of ≥24 for participants with 13+ years education or ≥ 22 for participants with ≤ 12 years education, modified Hachinski score ≤ 4,[39] and confirmation of diagnostic impression by the study clinician based on test scores and clinical ratings. Of note, eligibility criteria for aMCI were modified from the initial protocol (developed in 2016) to increase the inclusion of adults with earlier stage disease (i.e., 2016 inclusion criteria based on delayed recall on Logical Memory and the Auditory Verbal Learning Test were dropped). Other key eligibility criteria included being willing and able to safely participate, be randomized to either intervention, travel to the YMCA 4 times/week, and have an available study partner. People were excluded if they were found to have significant neurologic disease other than aMCI, history of significant psychiatric disease within the previous 12 months, history of significant cardiovascular events (e.g., myocardial infarction, coronary artery angioplasty, bypass grafting, STENT) within the previous 6 months, alcohol or substance abuse within the previous 2 years, hemoglobin A1c levels ≤ 7, insulin use for type 2 diabetes, use of psychoactive medications within 60 days of screening, or past use of anti-amyloid medications. All screened individuals provided informed consent. EXERT enrollment timeline and cohort characteristics are published.[36]

2.3 | EXERT interventions

2.3.1 | AX and SBR intervention arms

Both groups completed their assigned interventions at local participating YMCAs 4 times/week for 45 min/session. Frequency, duration,

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and intensity of the EXERT exercise programs were gradually increased over the first 6 weeks to build self-efficacy and stamina and to reduce risk of injury. A study-certified trainer provided supervision for the first eight sessions and then for two of the four weekly sessions through month 12. In months 13–18, participants had the opportunity to continue their assigned exercise programs at the YMCA but without supervision. Prior to participant contact, trainers were centrally trained and certified on the study protocol, data collection, and adverse event (AE) recording and reporting and received training about aMCI/AD and daily challenges for individuals living with memory loss. AX and SBR participants were provided with a digital wrist-worn heart rate (HR) monitor with a chest strap for HR tracking while exercising. Participants taking HR-lowering medications were instructed to rely more heavily on other measures to monitor effort such as breathing rate and difficulty of talking while exercising. All participants were trained to use the rating of perceived exertion (RPE) modified Borg scale (ratings range from 1 = very mild, to 10 = very, very hard) in the first 2 weeks of the program as an additional means of assessing exercise effort. Proper use of the RPE scale was assessed and retrained by the trainer at regular intervals and as needed throughout the study. Adherence was evaluated using HR monitoring, RPE, and trainer and participant records of completed exercise sessions. Trainer records of supervised sessions included date/time, time in target HR zone, HR logged at 5–10 min intervals, duration, trainer assessment of effort, and activity details (e.g., treadmill grade/speed; body parts stretched), which were entered into the ADCS Web-based electronic data capture (EDC) system for regular central review. Participants also kept a log of unsupervised exercise session details (duration, mean HR, maximum RPE, activity type) that was reviewed by the trainer during supervised sessions. The infrastructure to support fidelity of intervention delivery included centralized training and oversight and regular contact with clinic and YMCA teams. YMCA study staff also met monthly with the clinic YMCA Liaison and with the Intervention Oversight Team to review progress and challenges. The study adherence goal was for participants to complete ≥ 80% of their prescribed sessions (3.2 session/week) within their targeted HR zone. Multiple strategies were used to facilitate adherence (e.g., motivational interviewing, make-up sessions, group sessions, alternate exercise plans during travel, regular participant contact). When continuation of the intervention was deemed medically unsafe for a participant (e.g., after joint surgery or a fall), the intervention was temporarily discontinued. When the participant was cleared to restart the intervention, exercise was gradually re-introduced over 2–4 weeks. For these individuals, clinic visits were pushed back when necessary to provide at least 6 weeks of full intensity exercise prior to an outcomes assessment.

2.3.2 | AX arm

The AX intervention aligned with standard American College of Sports Medicine (ACSM) recommendations[40] and protocols tested in smaller-scale clinical trials.[20,21,41,42] The AX prescription targeted aerobic exercise for 45 min (includes warm-up and cool-down), 4 times/week, and was introduced gradually to AX participants by slowly increasing frequency and duration over the first 6 weeks to build self-efficacy and stamina, and to reduce risk of injury. Aerobic training targeting moderate-high cardiorespiratory intensity (70%–80% of heart rate reserve [HRR]; HRR = 220-age-resting HR; target heart rate range = [HRR x 0.70]+resting HR – [HRR x 0.80]+resting HR) was completed on a treadmill (most common), elliptical trainer, or stationary cycle.

2.3.3 | SBR arm

The SBR intervention included a rotating and varied routine of stretching exercises for large and small muscle groups and activities to improve balance and range of motion. The intensity goal of SBR activities was to maintain heart rate at or below 35% heart rate reserve for the 45 min sessions, 4 times/week (target heart rate < [HRR x 0.35]+resting HR). As with the AX, exercise frequency and duration were gradually increased over 6 weeks to promote self-efficacy and reduce injury risk.

2.4 | EXERT clinic visits

2.4.1 | Pre-screening visit

Prior to the clinic screening visit, verbal informed consent for pre-screening was obtained by interested candidates who completed a telephone interview to assess medical eligibility, presence of memory concerns, sedentary status (using EXERT-modified TAPA), willingness to follow the protocol, and availability of a study partner.

2.4.2 | Clinic screening visit

At the start of the screening visit, participants provided written informed consent. Screening procedures included medical history and medication review, physical and neurological examination, blood collection for clinical labs, biorepository, DNA banking, and APOE genotyping, electrocardiogram, cognitive assessment (MMSE and expanded mental status exam [3MSE], Story Recall, Auditory Verbal Learning Test), behavioral/functional assessment (CDR, Cognitive Change Index, Geriatric Depression Scale), 400 m Walk Test, and brain magnetic resonance imaging (MRI). Participants meeting all eligibility criteria were scheduled for the baseline assessment. These individuals were provided with a wrist-worn actigraph (ActiGraph Link) and a 10-day recording period was initiated (and completed prior to the baseline visit).

2.4.3 | Baseline

Baseline procedures included confirmation of eligibility, measurement of vital signs and weight, fasted blood collection for labs and storage, AE query, assessment of the primary cognitive outcome

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(ADAS-Cog-Exec; see below), assessment of secondary cognitive outcomes via iPad, behavioral/functional assessments, and completion of self-assessment questionnaires by the study partner. Upon completion of all baseline assessments, participants were randomized in a 1:1 fashion to either the AX or SBR group by the ADCS Data Core using a real-time Web-based system. A trained and certified unmasked clinic staff member disclosed randomization assignment, and participants signed a behavioral contract indicating their willingness to complete the prescribed activities.

2.4.4 | Follow-up visits (months 6, 12, 18)

Outcomes assessments completed at baseline (or screening) were also completed at follow-up visits. Brain MRI was conducted only during the month 12 follow-up visit, as it marked the end of the primary observation period with supervised exercise. For participants who asked to exit the study prior to the 12-month assessment, all outcomes were collected in an early termination visit.

2.5 | ADNI-1: Usual care comparison group

To identify an appropriate usual care comparison group for EXERT, we considered a number of existing observational study or placebo RCT cohorts with similar 12-month longitudinal cognitive data, including ADNI-1, National Alzheimer's Coordinating Center data, and the Vitamin E and Donepezil trial.[43] ADNI-1 was selected given the similarities in cohort characteristics (e.g., age, cognitive status) and, importantly, availability of specific cognitive test scores to permit construction of the ADAS-Cog-Exec composite, the primary outcome in EXERT (see Section 2.6).

ADNI-1 was launched in 2003 as a longitudinal study among academic institutions in the United States and Canada to study the natural progression leading to AD; to develop clinical, imaging, genetic, and biochemical markers for early detection and disease progression; and to provide a widely accessible data repository to advance the science, including clinical trials. Data for the present analyses were obtained from the ADNI database. [34,44] In total, 819 participants (229 cognitively normal, 398 aMCI, and 192 AD) were enrolled into ADNI-1 across 57 sites and followed for 12 months using standardized cognitive measures, including Digit Span, Category Fluency, Trail-Making A and B, ADAS-Cog, and the CDR.[34,45] All enrolled ADNI-1 participants carried a diagnosis of aMCI.[46]

2.6 | Cognitive endpoint: ADAS-Cog-Exec

The primary outcome for EXERT was a global cognition composite measure, the ADAS-Cog-Exec, which was constructed and validated based on prior evidence and hypotheses about the sensitivity of the specific components to exercise effects in older adults (executive function) and to longitudinal change in adults with aMCI. Details about composite construction and validation are published.[35] The ADAS-Cog-Exec includes the following measures with sensitivity to early changes in cognitive function with disease progression: select subscales of the ADAS-Cog13 (Word Recall, Delayed Word Recall, Orientation, Number Cancellation); supplemental executive function measures (Trail-Making Test A&B, time to completion; Digit Symbol Substitution Test, total correct; Category Fluency, mean of Animals and Vegetables); and box scores for the cognitive components of the CDR (i.e., Memory, Orientation, Judgement & Problem Solving).[35,47] For this investigation, we examined ADAS-Cog-Exec using baseline-to-month 12 change scores, consistent with the approach used in the main EXERT trial and in the development and validation of the ADAS-Cog-Exec.[35]

2.7 | Brain imaging

2.7.1 | Outcomes

Brain MRI volumes in specific brain regions were compared across EXERT and the matched ADNI-1 usual care groups, including (1) hippocampus; (2) prefrontal composite (meta-region of interest [ROI] sum of cortical thickness in superior frontal, caudal-middle frontal, rostral-middle frontal, pars opercularis, and pars triangularis regions); and (3) AD signature composite (meta-ROI sum of cortical thickness in parahippocampus, fusiform, inferior temporal, middle temporal, and inferior-parietal regions), which were the main imaging outcomes in EXERT. We also examined ADNI-1 versus EXERT on secondary EXERT imaging outcomes, including total gray matter volume, lateral ventricular volume, and entorhinal cortex volume.

2.7.2 | MRI data collection and processing

The ADNI imaging protocol is described elsewhere.[48,49] Briefly, structural brain images were acquired using 1.5-T MRI imaging systems with T1-weighted MRI scans. For each participant, two T1-weighted MRI scans were collected using a sagittal volumetric magnetization prepared rapid gradient echo (3D MPRAGE) sequence with the following acquisition parameters: echo time (TE) of 4 ms, repetition time (TR) of 9 ms, flip angle of 8°, and acquisition matrix size of $256 \times 256 \times 166$ in the *x*-, *y*- and *z*-dimensions with a nominal voxel size of 0.94 mm × 0.94 mm × 1.2 mm. The MPRAGE image with higher quality was selected based on standardized criteria at the ADNI MRI quality control center at the Mayo Clinic (Rochester, MN, USA).

For EXERT, structural MRI procedures were overseen by the ADCS Imaging Core. Arterial spin labeling (ASL) MRI was overseen by the Imaging Core and Wake Forest University School of Medicine. We supported MRI data collection across three scanner types in EXERT for the collection of high-resolution images for volumetric analyses (Table S1). Phantom scans were performed at each site to standardize acquisition parameters across scanners. Each scanner was certified following the completion of qualifying protocols. MRI included a localizer scan, followed by a high-resolution 3D T1 structural series (MPRAGE

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or inversion recovery-spoiled gradient recalled [IR-SPGR]), a T2-weighted series (fluid-attenuated inversion recovery [FLAIR]), a diffusion weighted scan, and a gradient recalled echo scan. Sites with access to approved 3T scanners also included a resting-state ASL MRI series, appended to the MRI protocol. Standard rigorous procedures were used to ensure high data integrity. Baseline and follow-up datasets for each participant underwent spatial rigid body co-registration followed by nonlinear registration and neuroanatomic parcellation to quantify whole-brain and subregional volumetric change on a participant-by-participant basis. Corrections were made for gradient nonlinearities and intensity non-uniformity. A clinical read of the MRI confirmed eligibility.

For EXERT and ADNI-1 samples, T1 images from baseline and month 12 were used to construct the composite imaging measures. Images were processed using the longitudinal stream of Freesurfer version 7.1.1.[50,51] Robust, inverse consistent registration was used to create an unbiased within-subject template space and image. Common information from the within-subject template was used for processing (e.g., skull stripping, Talairach transforms, atlas registration) and initializing spherical surface maps and parcellations. Regional thicknesses for prefrontal and AD signature meta-regions and hippocampal volumes were calculated using the Desikan-Killiany atlas.[52]

2.8 | Statistical analysis

The modified intent to treat (mITT) population was used for the AX and SBR arms, consistent with the approach used for the main EXERT trial. The mITT population included all eligible individuals who (1) initiated the exercise intervention and (2) completed at least one post-baseline assessment at months 6 or 12. Participants in each EXERT arm were frequency matched using propensity score methods (i.e., greedy nearest neighbor matching) to ADNI-1 participants according to age, sex, self-identified race, self-identified ethnicity, education, apolipoprotein E (APOE) ε4 genotype, and baseline MMSE.[53] Matching calipers were created using a generalized linear model and were set at a maximum width of 0.25, as previously recommended (i.e., propensity scores for pairs differed by at most 0.25).[53,54] Within the caliper, the nearest neighbor for each EXERT participant was determined using Mahalanobis distance matching. Matching was performed using the MatchIt package in R.[55] ADNI-1 did not collect information on physical activity; thus, we were unable to determine or match on baseline sedentary status in ADNI-1 participants.

We compared baseline characteristics between EXERT and ADNI-1 using Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. Comparisons of changes in ADAS-Cog-Exec from baseline to month 12 for each EXERT arm relative to its matched ADNI-1 group were examined using linear regression models. Comparisons of 12-month changes in the three brain imaging outcomes between groups were evaluated using linear regression models. Confounders including age, sex, race, ethnicity, education, APOE ε4 genotype, and baseline MMSE were considered for inclusion in the models if, following propensity score matching, the following conditions were met: (1) imbalance of the covariate at baseline ($p < 0.1$) and (2) $p < 0.15$ for the association between the covariate and outcome (i.e., change in ADAS-Cog-Exec or brain imaging measure). p-Values were considered statistically significant at $p < 0.05$. Statistical analyses were performed in *R* version 4.2.2.

3 | RESULTS

3.1 | Comparison of EXERT arms to matched ADNI-1 participants on baseline characteristics

3.1.1 | Before matching

A total of 296 individuals were randomized into EXERT. The EXERT AX arm ($n = 124$) had a lower proportion of males, higher MMSE, and lower proportion of APOE ε4 carriers than the overall cohort of ADNI-1 participants with aMCI ($n = 356$) (Table S2). There were no significant differences in age, race, ethnicity, or education. The EXERT SBR arm ($n = 126$) had a lower proportion of males, higher proportion of Black participants, lower proportion of Hispanic/Latino participants, higher education level, higher MMSE, and lower proportion of APOE ε4 carriers than the overall ADNI-1 cohort with aMCI (Table S3). There were no significant group differences in age.

3.1.2 | After matching

109 pairs were matched for EXERT AX and ADNI-1, and 105 pairs were matched for EXERT SBR and ADNI-1; 81 ADNI-1 participants were paired with participants in both groups. The EXERT AX and ADNI-1 pairs included 1.8% and 1.8% Asian, 5.5% and 4.6% Black or African American, 92.7% and 93.6% White, and 1.8% and 0.9% Hispanic or Latino, respectively. The EXERT SBR and ADNI-1 pairs included 1.0% and 2.9% Asian, 1.9% and 5.7% Black or African American, and 97.1% and 91.4% White, respectively; no Hispanic or Latino individuals were included. AX and SBR groups did not significantly differ from their respective matched ADNI-1 groups in age, sex, race, ethnicity, education, MMSE, or APOE ε4 genotype (Tables 1 and 2).

3.2 | Comparison of EXERT arms to matched ADNI-1 participants on ADAS-Cog-Exec

The EXERT AX group showed significantly less 12-month cognitive decline as measured by the ADAS-Cog-Exec than did the matched ADNI-1 group ($\beta = 0.169$; 95% confidence interval [CI], 0.011 to 0.328; $p = 0.036$) (Figure 1). The EXERT SBR group also showed significantly less 12-month cognitive decline as measured by the ADAS-Cog-Exec than did its matched ADNI-1 group ($\beta = 0.181$; 95% CI, 0.007 to 0.354; $p = 0.041$) (Figure 1).

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TABLE 1 Participant characteristics in ADNI-1 and EXERT AX after propensity score matching.

Variable	ADNI-1 (*N* = 109)	EXERT AX (*N* = 109)	*p*-Value
Gender			>0.99
Female	52 (47.7%)	52 (47.7%)	
Male	57 (52.3%)	57 (52.3%)	
Age (years)	75.3 (6.88)	74.7 (5.82)	0.183
Race			>0.99
Asian	2 (1.8%)	2 (1.8%)	
Black or African American	6 (5.5%)	5 (4.6%)	
White	101 (92.7%)	102 (93.6%)	
Ethnicity			>0.99
Hispanic or Latino	2 (1.8%)	1 (0.9%)	
Not Hispanic or Latino	106 (97.2%)	107 (98.2%)	
Unknown or not reported	1 (0.9%)	1 (0.9%)	
Education	16.0 (2.85)	16.4 (2.27)	0.441
MMSE	27.7 (1.63)	27.9 (1.88)	0.113
APOE4			
Carrier	30 (27.5%)	30 (27.5%)	>0.99
Non-carrier	79 (72.5%)	79 (72.5%)	

Note: *p*-Value corresponds to Wilcoxon Rank sum test statistics for continuous variables and Fisher's exact test statistics for categorical variables. Participants in each EXERT arm were frequency matched with propensity score methods to ADNI-1 participants according to age, sex, race, ethnicity, education, APOE ε4 genotype, and baseline MMSE.
Abbreviation: ADNI-1, Alzheimer's Disease Neuroimaging Initiative 1; APOE4, apolipoprotein E4; MMSE, Mini-Mental State Examination.

TABLE 2 Participant characteristics in ADNI-1 and EXERT SBR after propensity score matching.

Variable	ADNI-1 (*N* = 105)	EXERT SBR (*N* = 105)	*p*-Value
Gender			0.89
Female	49 (46.7%)	51 (48.6%)	
Male	56 (53.3%)	54 (51.4%)	
Age (years)	75.5 (7.48)	75.1 (6.47)	0.282
Race			0.23
Asian	1 (1.0%)	3 (2.9%)	
Black or African American	2 (1.9%)	6 (5.7%)	
White	102 (97.1%)	96 (91.4%)	
Ethnicity			>0.99
Not Hispanic or Latino	104 (99.0%)	103 (98.1%)	
Unknown or not reported	1 (1.0%)	2 (1.9%)	
Education	16.1 (2.77)	16.2 (2.31)	0.816
MMSE	28.0 (1.67)	28.0 (1.93)	0.629
APOE4			
Carrier	27 (25.7%)	29 (27.6%)	0.876
Non-carrier	78 (74.3%)	76 (72.4%)	

Note: *p*-Value corresponds to Wilcoxon rank sum test statistics for continuous variables and Fisher's exact test statistics for categorical variables. Participants in each EXERT arm were frequency matched with propensity score methods to ADNI-1 participants according to age, sex, race, ethnicity, education, APOE ε4 genotype, and baseline MMSE.
Abbreviation: ADNI-1, Alzheimer's Disease Neuroimaging Initiative 1; APOE4, apolipoprotein E4; MMSE, Mini-Mental State Examination; SBR, stretching, balance, and range of motion.

3.3 | Comparison of EXERT arms to matched ADNI-1 participants on brain imaging

Among the 109 matched pairs for EXERT AX and ADNI-1, 84 participants in the AX group and 107 participants in the ADNI-1 group had brain imaging measures available for analysis (Table S4). Among the 105 matched pairs for EXERT SBR and ADNI-1, 75 participants in the SBR group and 99 participants in the ADNI-1 group had brain imaging measures available for analysis (Table S5). Age and MMSE differed between EXERT AX and ADNI-1 following matching; models comparing EXERT arms with ADNI-1 on neuroimaging outcomes were adjusted for these variables.

There were no significant 12-month differences in hippocampal volume ($\beta = 6.27$; 95% CI, −46.19 to 58.74; $p = 0.81$) or AD composite cortical thickness ($\beta = 0.09$; 95% CI, −0.06 to 0.25; $p = 0.25$) between the EXERT AX and ADNI-1 groups (Figure 2). There was a trend toward less loss of prefrontal cortical thickness for the EXERT AX group relative to the ADNI-1 group ($\beta = 0.19$; 95% CI, −0.02 to 0.39; $p = 0.08$). There were no significant differences between EXERT AX and ADNI-1 groups in 12-month change on secondary EXERT imaging outcomes of lateral ventricular volume ($\beta = 138.80$; 95% CI, −630.44 to 908.03; $p = 0.72$) or total gray matter volume ($\beta = 143.87$; 95% CI, −3498.44 to 3786.19; $p = 0.94$), but the EXERT AX group had significantly less entorhinal cortex volume loss ($\beta = 73.64$; 95% CI, 27.55 to 119.72, $p = 0.002$; Figure 2).

There was no significant 12-month difference between the EXERT SBR and ADNI-1 groups in hippocampal volume ($\beta = -2.58$; 95% CI, −58.25 to 53.10; $p = 0.93$; Figure 3). There were trends suggesting less decline in AD composite cortical thickness in the EXERT SBR group than the ADNI-1 group ($\beta = 0.16$; 95% CI, −0.004 to 0.321; $p = 0.06$) and prefrontal composite cortical thickness ($\beta = 0.21$; 95% CI, −0.034 to 0.461; $p = 0.09$) measures. There were no significant differences between the EXERT SBR and ADNI-1 groups in 12-month change on secondary EXERT imaging outcome measures of total gray matter volume ($\beta = -486.2$; 95% CI, −4369.30 to 3396.92; $p = 0.81$), lateral ventricular volume ($\beta = -74.14$; 95% CI, −770.83 to 622.55, $p = 0.83$) or entorhinal cortex volume ($\beta = 16.87$; 95% CI, −28.35 to 62.0; $p = 0.46$) (Figure 3).

4 | DISCUSSION

EXERT AX and SBR showed significantly less decline on a global measure of cognitive function during the 12-month intervention than similar adults with aMCI in ADNI-1. There were no significant

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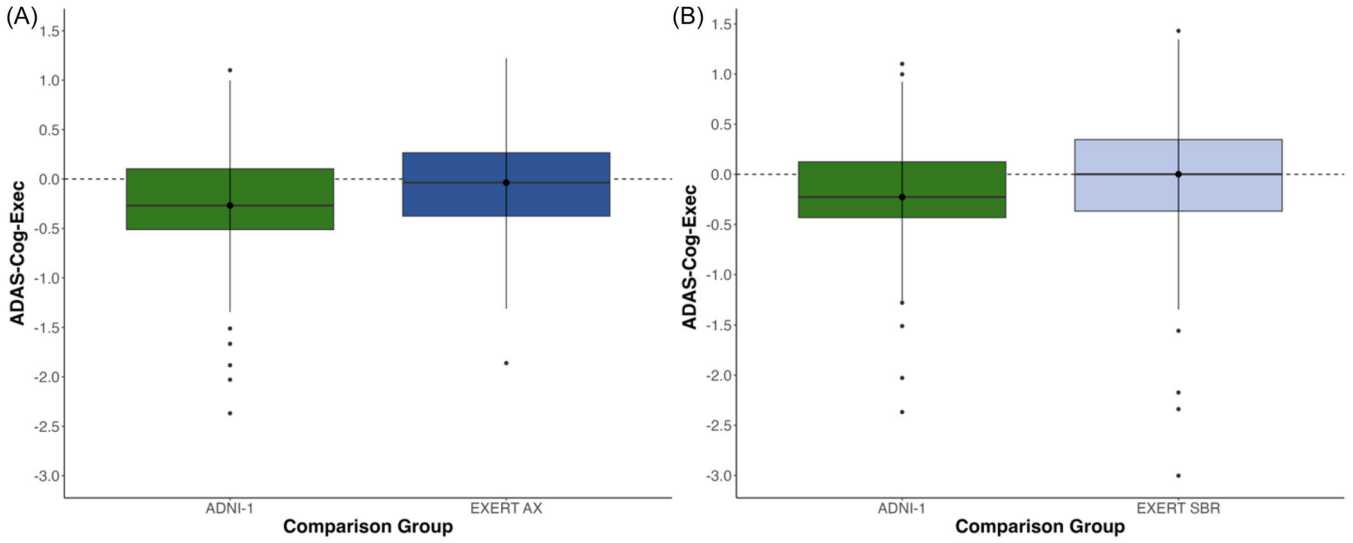

FIGURE 1 Comparison of mean 12-month change in ADAS-Cog-Exec between EXERT AX and SBR arms versus matched ADNI-1 participants. The primary outcome for EXERT was a global cognition composite measure, the ADAS-Cog-Exec, which was constructed and validated based on prior evidence and hypotheses about sensitivity of the specific components to exercise effects in older adults (executive function) and to longitudinal change in adults with aMCI. Participants in each EXERT arm were frequency matched using propensity score methods to ADNI-1 participants according to age, sex, race, ethnicity, education, APOE ε4 genotype, and baseline MMSE. ADAS, Alzheimer's Disease Assessment Scale; ADNI-1, Alzheimer's Disease Neuroimaging Initiative 1; APOE, apolipoprotein E; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; SBR, stretching, balance, and range of motion.

12-month differences in primary brain imaging outcomes between EXERT and ADNI-1. There was significantly less entorhinal cortex volume loss in EXERT AX versus ADNI-1. Findings suggest that both the moderate-high and low-intensity EXERT exercise interventions provided some protection against cognitive decline in older adults with aMCI relative to usual care.

The topline results of EXERT indicated no intervention group difference in ADAS-Cog-Exec after 12 months of moderate-high or low intensity exercise (Baker et al., in press). However, neither group showed the decline from baseline expected in an aMCI cohort.[56] We observed that ADAS-Cog-Exec declined over 12 months in adults with aMCI similar to those enrolled in EXERT who received no intervention (usual care). This demonstrates the level of expected decline in an untreated EXERT aMCI cohort and shows that ADAS-Cog-Exec was sensitive to the expected decline. A recent meta-analysis of 20 RCTs in 1393 participants found that a multi-component exercise intervention had greater cognitive benefit relative to aerobic exercise alone and that exercise of 35 to 50 minutes per session, 3 to 5 times/week, and for more than 4 months (i.e., the same frequency and duration in EXERT) showed the greatest benefit.[57] This finding suggests that frequency and duration of exercise, rather than intensity per se, may play an important role in stalling cognitive decline. Similar to EXERT, a recent 1-year intervention among 73 sedentary older adults observed no difference in cognition between the aerobic exercise and stretching/toning arms, with both groups showing an increase in the cognitive composite score.[58] Overall, our finding of no decline in either AX or SBR suggests that regular (3–4 times/week for 12 months), trainer-supported exercise of any intensity likely stalled cognitive decline in adults with aMCI.

It is possible that additional social interaction with research staff during participation in any intervention trial, regardless of intervention type, slows or stalls cognitive decline. Participants in trials such as EXERT are exposed to a greater degree of study-related social interaction than participants in ADNI-1, and this difference could have contributed to the intervention versus usual care effect we observed. EXERT and ADNI-1 were similar in their assessment protocols, whereas in EXERT, the intervention may have added at least 50 additional hours of contact with YMCA trainers. There are other RCTs in aMCI cohorts requiring more social contact with research staff than ADNI-1, yet many of these trials still show the expected decline in cognition among those assigned to placebo.[43,59,60] Thus, simply being enrolled in an intervention study does not necessarily stall cognitive decline. The EXERT design intentionally equated social contact with clinic staff and trainers for AX and SBR so that any difference in intervention response could be attributed to exercise mode or level of cardiorespiratory exercise intensity. While the social contact component of EXERT may partially account for stalled cognitive decline in both arms versus ADNI-1, a number of other RCTs[14,19–29] have demonstrated benefits of regular physical activity on cognition, suggesting that regular supervised exercise in EXERT slowed cognitive decline.

Our findings support the beneficial effects of exercise on cognition in adults with aMCI. A 6-month aerobic exercise and strength training intervention among 170 older adults with memory impairment found a 0.26-point improvement on the ADAS-Cog in the intervention group and a 1.04 point deterioration in an education and usual care group over 6 months (absolute difference, −1.3 points [95% CI, −2.38 to −0.22]).[21] The beneficial effects of exercise persisted at an attenuated level over a longer follow-up period (mean difference, 0.69 points at 18

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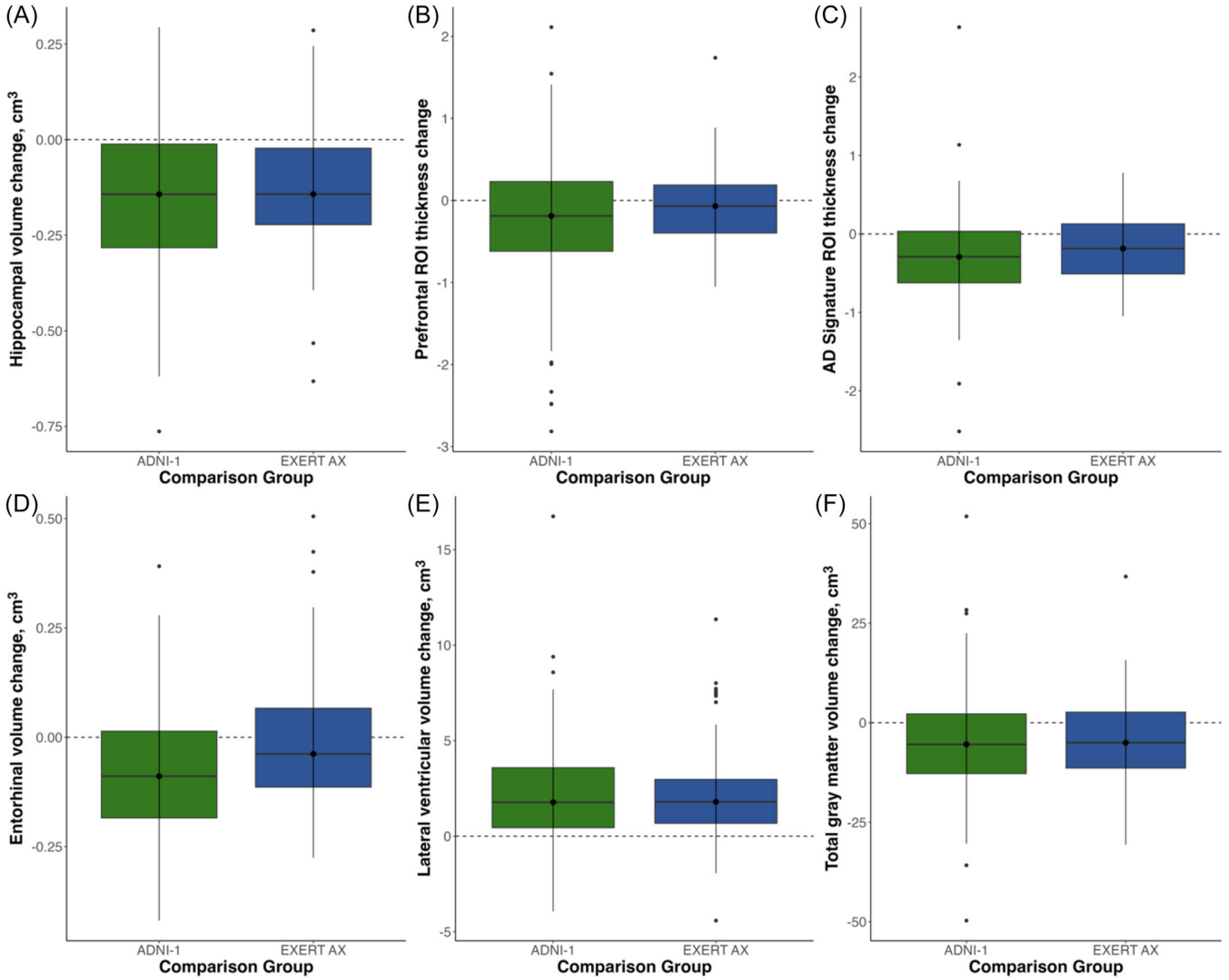

FIGURE 2 Comparison of mean 12-month change in brain imaging outcomes between EXERT AX and matched ADNI-1 participants. Participants in each EXERT arm were frequency matched using propensity score methods to ADNI-1 participants according to age, sex, race, ethnicity, education, APOE ε4 genotype, and baseline MMSE. ADNI-1, Alzheimer's Disease Neuroimaging Initiative 1; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination.

months), and results were similar among those with a clinical diagnosis of MCI. Another 6-month RCT among 100 adults with MCI found that a multicomponent exercise intervention had no greater cognitive benefit than an education and usual care control condition, but did have a significantly greater benefit on cognition in those with aMCI.[22] The EXERT trial, in contrast, compared two levels of exercise intensity and developed, optimized, and validated the ADAS-Cog-Exec to detect subtle cognitive changes over time in adults with aMCI.[35] The findings from EXERT suggest that regular supervised exercise of any intensity, either low or high, may provide cognitive benefits over usual care for older adults with aMCI.

EXERT and matched ADNI-1 groups did not differ in 12-month change on primary volumetric MRI outcome measures. Both AX and SBR showed trends for less loss in prefrontal cortex relative to ADNI-1, consistent with previous studies showing that 6 months of aerobic exercise in sedentary older adults was associated with increased gray and white matter volumes in the prefrontal and temporal cortices (vs. a stretching and toning intervention), regions that have been linked to age-related decline in executive function and memory.[18,41] ADAS-Cog-Exec was empirically developed to increase weighting on executive function, a frontal cortex-mediated cognitive domain that has been shown to benefit from aerobic exercise.[14] Less loss of prefrontal cortex thickness with exercise may reflect regional biological benefits of exercise (e.g., increased blood flow to long but small diameter vessels in these regions) that positively impact cognition. Although positive effects of aerobic exercise on hippocampal volume have been previously observed,[28] we did not observe this effect in the present study, like others.[61,62] However, we observed significantly less entorhinal cortex volume loss over 12 months in EXERT AX than ADNI-1. Entorhinal cortex atrophy in individuals with MCI is associated with progression to AD, perhaps even more strongly than hippocampal atrophy.[63–65] Thus, differences in entorhinal cortex atrophy in EXERT

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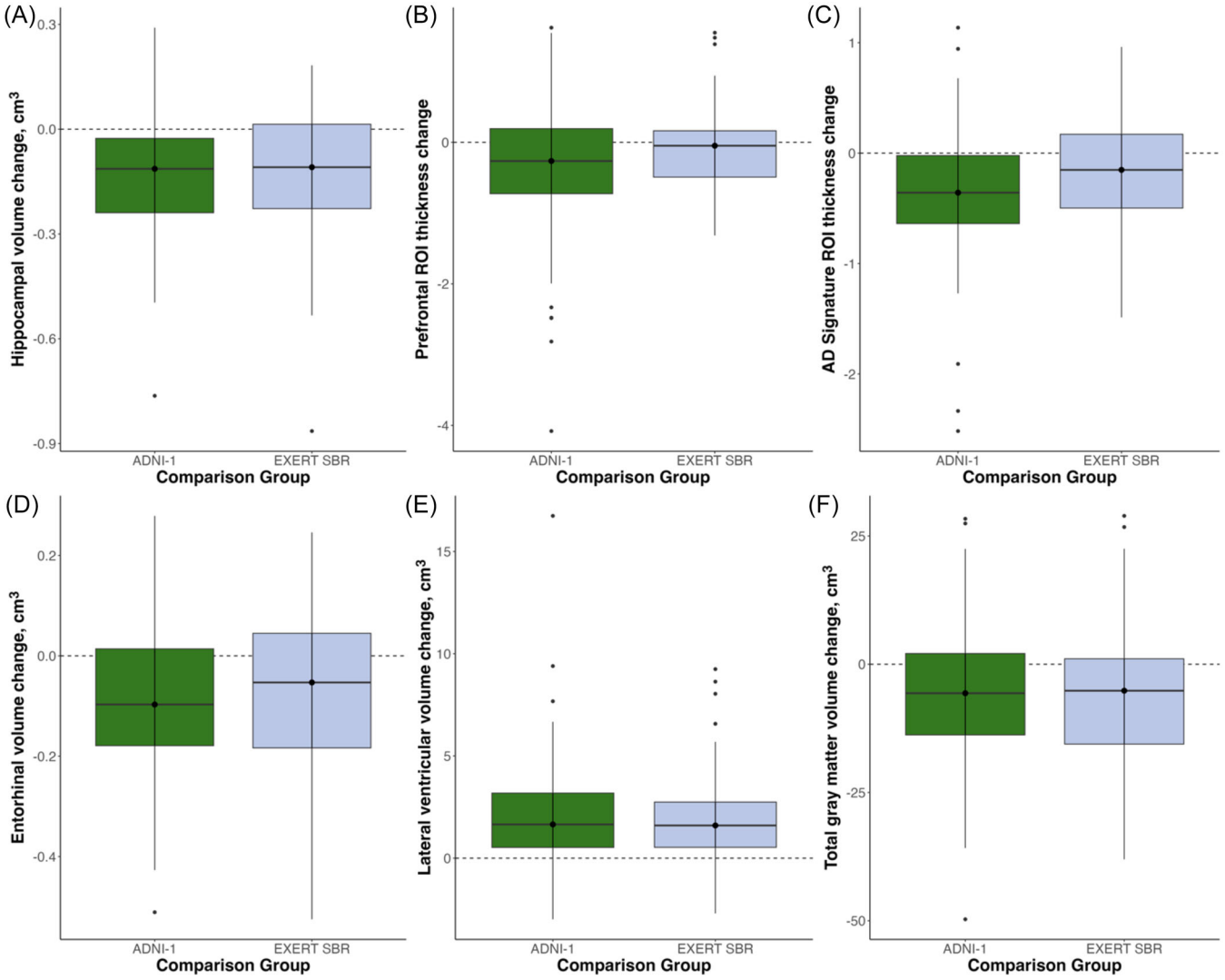

FIGURE 3 Comparison of mean 12-month change in brain imaging outcomes between EXERT SBR and matched ADNI-1 participants. Participants in each EXERT arm were frequency matched using propensity score methods to ADNI-1 participants according to age, sex, race, ethnicity, education, APOE ε4 genotype, and baseline MMSE. ADNI-1, Alzheimer's Disease Neuroimaging Initiative 1; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; SBR, stretching, balance, and range of motion.

AX versus ADNI-1 may have contributed to the observed differences in 12-month change on the ADAS-Cog-Exec outcome measure.

The lack of alignment between cognitive and brain imaging results in our comparisons (i.e., a decrease in cognitive decline vs. no significant change in brain volume decline) is similar to reports in other RCTs, many of which observed changes in brain volume but no change in cognitive function.[66–68] There remains continuing uncertainty about the misalignment of clinical and biomarker results in MCI and AD trials; caution is warranted when interpreting findings.

A limitation of our study is absence of a randomized placebo group drawn from the same population as those randomized to receive the interventions. EXERT was developed to balance early community feedback regarding willingness to participate in a usual care group, the need to examine exercise intensity effects while keeping social contact constant, and budgetary constraints that could accommodate only two intervention groups. To address this, we made an a priori decision to leverage rich data resources available through ADNI to examine EXERT intervention effects relative to a propensity matched cohort from ADNI-1 that could serve as a no intervention usual care comparator. ADNI-1 was selected given the similar characteristics of the cohort to EXERT and due to the availability of baseline and 12-month observational data for the same cognitive (e.g., ADAS-Cog-Exec) and MRI volumetric measures examined in EXERT. It is possible that EXERT and ADNI-1 participants differed on sedentariness, a key characteristic that could confer cohort-related bias in our results. However, given the high prevalence of sedentary behavior in older adults (67% are sedentary for > 8.5 h/day),[69] presumably including those in the ADNI-1 cohort, the potential impact of this bias may be minimal. This potential bias is further minimized by the finding that EXERT participants were sedentary, and these were the individuals who failed to show decline. If sedentary ADNI-1 participants could have been included in the comparison sample, the magnitude of difference between EXERT and

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ADNI-1 may have been greater. An important strength of EXERT was that the two interventions had similar levels of social contact, which was especially salient during the coronavirus disease 2019 (COVID-19) pandemic when older adults may have experienced social isolation during the conduct of the trial. It is possible that the differences we observed may be due to healthy recruitment bias, with healthier individuals self-selecting to join EXERT relative to ADNI-1; however, we matched participants on key baseline characteristics (e.g., MMSE), and EXERT participants were all sedentary (an independent risk factor for poor health outcomes),[70] making this an unlikely explanation of our findings. It is possible that the absence of differences in MRI outcomes may be partly attributable to differences in acquisition and processing parameters between EXERT and ADNI-1, given that ADNI-1 employed older methods to measure MRI outcomes with reduced precision of volumetric estimates.

Our findings suggest that 12 months of regular supervised moderate-high or low intensity exercise in the EXERT trial slowed cognitive decline in older adults with aMCI relative to the expected cognitive decline observed with usual care in the ADNI-1 longitudinal observational study. The potential protective effect of supported low intensity as well as moderate-high intensity exercise relative to usual care increases the feasibility and probability of the adoption of an exercise intervention in the wider community of older adults living with multiple physical and life challenges that may preclude adoption and adherence to a moderate-high intensity physical activity program.

AUTHOR CONTRIBUTIONS

Concept and design: Shadyab, Jacobs, Thomas, Salmon, LaCroix, Feldman, Baker. *Acquisition, analysis, or interpretation of data*: Shadyab, Aslanyan, Jacobs, Salmon, Morrison, Katula, Jin, Thomas, LaCroix, Pa, Cotman, Feldman, Baker. *Statistical analysis*: Aslanyan. *Manuscript development*: Shadyab, Baker.

Other Contributions:

Leadership. The EXERT trial was supported by an NIH/NIA U19 award (AG010483) to the Alzheimer's Disease Cooperative Study (ADCS: Principal Investigators: Howard Feldman, MDCM; Judy Pa, PhD). U19 Project 2 (EXERT) Directors were Laura D. Baker, PhD and Carl W. Cotman, PhD. Overall conduct of the trial was coordinated through the ADCS, and intervention design and delivery were overseen by Wake Forest University School of Medicine: Jeffrey Katula, PhD; Elizabeth Chmelo, MS; Barbara Nicklas, PhD; and Cara Johnson, MA, in partnership with the YMCA of the USA: Heather Hodge, MEd; Valerie Lawson, MS RD; and Cara R. Johnson. The study team is grateful to Dr. Paul Aisen for his vision and leadership to facilitate inclusion of a large exercise RCT as part of the original multi-project ADCS U19 grant submission to NIH.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All study participants provided written, informed consent. Study partners also provided written consent. The study was approved by each participating institution's Institutional Review Board and was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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