

# UC Irvine

## UC Irvine Previously Published Works

### Title

Recruitment of a multi-site randomized controlled trial of aerobic exercise for older adults with amnesic mild cognitive impairment: The EXERT trial

### Permalink

<https://escholarship.org/uc/item/8hg3s1wn>

### Journal

Alzheimer's & Dementia, 17(11)

### ISSN

1552-5260

### Authors

Shadyab, Aladdin H  
LaCroix, Andrea Z  
Feldman, Howard H  
et al.

### Publication Date

2021-11-01


### DOI

10.1002/alz.12401

Peer reviewed

## FEATURED ARTICLE

# Recruitment of a multi-site randomized controlled trial of aerobic exercise for older adults with amnesic mild cognitive impairment: The EXERT trial

Aladdin H. Shadyab<sup>1</sup>  | Andrea Z. LaCroix<sup>1</sup> | Howard H. Feldman<sup>2</sup> | Christopher H. van Dyck<sup>3</sup> | Ozioma C. Okonkwo<sup>4</sup> | Steven P. Tam<sup>5</sup> | J. Kaci Fairchild<sup>6</sup> | Kathleen A. Welsh-Bohmer<sup>7</sup> | Genevieve Matthews<sup>2</sup> | Daniel Bennett<sup>2</sup> | Alexandre A. Shadyab<sup>2</sup> | Kimberly A. Schafer<sup>2</sup> | Rosemary H. Morrison<sup>2</sup> | Sean A. Kipperman<sup>2</sup> | Jennifer Mason<sup>2</sup> | Donna Tan<sup>2</sup> | Ronald G. Thomas<sup>1,2</sup> | Carl W. Cotman<sup>8</sup> | Laura D. Baker<sup>9</sup> | for the ADCS EXERT Study Group

<sup>1</sup> Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, California, USA

<sup>2</sup> Department of Neurosciences, Alzheimer's Disease Cooperative Study, University of California, San Diego, La Jolla, California, USA

<sup>3</sup> Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA

<sup>4</sup> School of Medicine and Public Health, Wisconsin Alzheimer's Disease Research Center, University of Wisconsin-Madison, Madison, Wisconsin, USA

<sup>5</sup> University of California, Irvine School of Medicine, Irvine, California, USA

<sup>6</sup> Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, USA

<sup>7</sup> Department of Neurology, Bryan Alzheimer's Disease Research Center, Duke University School of Medicine, Durham, North Carolina, USA

<sup>8</sup> Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, California, USA

<sup>9</sup> Department of Internal Medicine-Geriatrics, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

## Correspondence

Aladdin H. Shadyab, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, 9500 Gilman Drive #0725, La Jolla, CA 92093, USA.  
Email: [ahshadya@health.ucsd.edu](mailto:ahshadya@health.ucsd.edu)

## Funding information

National Institutes of Health, National Institute on Aging, Grant/Award Number: U19 AG010483

## Abstract

**Introduction:** Effective strategies to recruit older adults with mild cognitive impairment (MCI) into nonpharmacological intervention trials are lacking.

**Methods:** Recruitment for EXERT, a multisite randomized controlled 18-month trial examining the effects of aerobic exercise on cognitive trajectory in adults with amnesic MCI, involved a diverse portfolio of strategies to enroll 296 participants.

**Results:** Recruitment occurred September 2016 through March 2020 and was initially slow. After mass mailings of 490,323 age- and geo-targeted infographic postcards and brochures, recruitment rates increased substantially, peaking at 16 randomizations/month in early 2020. Mass mailings accounted for 52% of randomized participants, whereas 25% were recruited from memory clinic rosters, electronic health records, and national and local registries. Other sources included news broadcasts, public service announcements (PSA), local advertising, and community presentations.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

**Discussion:** Age- and geo-targeted mass mailing of infographic materials was the most effective approach in recruiting older adults with amnesic MCI into an 18-month exercise trial.

**KEYWORDS**

Alzheimer's disease, clinical trial, exercise, lifestyle intervention, mild cognitive impairment, non-pharmacological, recruitment

## 1 | INTRODUCTION

Successful recruitment of adults with mild cognitive impairment (MCI) into clinical trials requires innovative strategies, given the number of challenges to identify these individuals in community settings. Recruitment of adults with MCI into nonpharmacological trials is particularly difficult, given the additional study demands associated with adherence to a behavioral intervention.<sup>1-4</sup> Barriers to recruitment of adults with MCI into such trials include stringent medical eligibility criteria and the time and effort required of participants that could impact motivation to enroll.<sup>1-4</sup> Individuals recruited from memory clinics versus the community tend to have more advanced MCI and may not be representative of the broader population of adults with early-stage MCI.<sup>2,5</sup> Severity of cognitive impairment in the study sample could impact the participant's ability to adhere to a complex intervention and the expected cognitive trajectory.<sup>5-7</sup> Mild impairments in cognitive function are frequently not identified through routine clinical care, which renders recruitment using diagnostic characterization ineffective for a large number of study candidates.<sup>8</sup>

Strategies to effectively recruit adults with MCI into nonpharmacological trials are not well documented. Given the increasing focus on the potential benefits of lifestyle interventions for AD prevention, it is imperative that we rely on recruitment science to identify, refine, and test new approaches that can support successful and timely enrollment of adults at high risk for dementia into promising trials. We describe the successes and challenges we encountered in recruiting adults with MCI into the EXERT trial.

## 2 | METHODS

### 2.1 | Overview of EXERT

EXERT is a multisite, randomized controlled 18-month study examining the effects of aerobic exercise versus stretching and balance on cognitive trajectory in sedentary older adults with amnesic MCI (aMCI; [clinicaltrials.gov: NCT02814526](https://clinicaltrials.gov/ct2/show/study/NCT02814526)). Participants are randomized to a moderate- to high-intensity aerobic training program or a stretching and balance program (control group). Participants complete the interventions with trainer supervision for 12 months at a local YMCA and without supervision for the final 6 months. The Alzheimer's Disease Cooperative Study (ADCS) at the University of California, San Diego serves as the central coordinating center, and Wake Forest School of Medicine oversees intervention delivery.

Key eligibility criteria included: 65 to 89 years old; Mini-Mental State Examination (MMSE) score  $\geq 24$  for  $\geq 13$  years of education or MMSE  $\geq 22$  for  $< 13$  years of education;<sup>9</sup> global Clinical Dementia Rating (CDR) of 0.5 with a memory score of  $\geq 0.5$ ;<sup>10</sup> modified Hachinski score  $\leq 4$ ;<sup>11</sup> largely sedentary according to the Telephone Assessment of Physical Activity (TAPA) questionnaire;<sup>12</sup> willing to travel to the YMCA four times per week for exercise; and availability of a study partner. All screened individuals provided informed consent.

### 2.2 | Recruitment methods

Recruitment occurred from September 2016 through March 2020. Several recruitment strategies were used to support 14 clinical sites, which all received institutional review board (IRB) approval. The recruitment target was 300 participants, with each site expected to recruit 22 participants. Participants self-reported their recruitment source at screening. Source statistics were carefully tracked with the rollout of each recruitment strategy.

#### 2.2.1 | Memory clinic patient rosters, patient registries, and electronic health records

Patient rosters from memory clinics, national and local registries, and electronic health records were accessed to identify potential participants. Individuals meeting preliminary eligibility criteria (e.g., age, no medical exclusions, evidence of cognitive impairment) were approached by mail and then by telephone to assess interest and continued eligibility.

#### 2.2.2 | Community outreach

Study teams at participating sites represented the study at senior health fairs and other community events and provided educational presentations to civic and faith-based groups, health-care providers, senior housing facilities, and advocacy groups.

#### 2.2.3 | Media outreach

Local newspapers published feature stories about the potential benefits of exercise for brain health that included a plug for EXERT.<sup>13-15</sup> National Public Radio (NPR) developed and broadcast a story about

EXERT ("Is Aerobic Exercise the Right Prescription for Staving Off Alzheimer's?"), which included interviews with study leadership and a study participant.<sup>16</sup> The story was disseminated widely across social media, including the Facebook pages of NPR, the ADCS, and the National Institute on Aging (NIA). Maria Shriver, broadcast journalist, recorded a 5-minute video endorsing EXERT. A short, edited version aired as a 1-minute public service announcement (PSA) on local TV stations and was shared on Facebook pages of EXERT sites (see <https://www.exertstudy.org>). Sites also relied on paid radio and television advertising.

### 2.2.4 | Age- and geo-targeted mass mailings

A total of 490,323 colorful infographic recruitment postcards or brochures were mailed on a quarterly basis from September 2017 through December 2019. A direct mail marketing company in San Diego, California, provided this service and used a commercially available, consumer-oriented mailing list compiled from public records. Mailings targeted adults 65 to 89 years old living within a specified geographical region defined by zip code and distance to a nearby participating YMCA (e.g., < 5 miles), given the study requirement to travel to the YMCA four times per week. To increase engagement of underrepresented groups, zip codes for communities with greater racial and ethnic diversity were oversampled. Postcards were developed centrally and refined through community focus groups and input from the study team; focus group feedback was not stored for qualitative analyses. Postcard infographics were designed to be culturally responsive in messaging and visual images (see [supporting information](#)).

### 2.2.5 | Centralized prescreening

To reduce screening burden on sites due to expected high response from mass mailings, the ADCS conducted centralized prescreening for six sites beginning in March 2019. A call center was established with a trained interviewer who assessed key eligibility criteria with interested candidates. Eligible candidates were referred to sites for further screening. IRB-approved procedures were used to transfer protected health information from the call center, and sites followed up with referrals within 48 hours.

## 3 | RESULTS

### 3.1 | Screen failures

A total of 992 individuals were screened during a brief telephone visit, which included 229 individuals referred from the central call center, with 457 (46.1%) deemed ineligible (Figure 1). Primary reasons for ineligibility included: (1) not sedentary (26.7%), (2) principal investigator (PI) discretion about safety or ability to meet other eligibility criteria (7.9%), (3) no study partner (7.0%), and (4) unwilling or unable to travel to the YMCA (5.9%). Among those eligible at the initial telephone screening visit (N = 535), 239 (44.7%) were deemed ineligible at the subsequent in-person screening visit. Primary reasons for ineligi-

### RESEARCH IN CONTEXT

- 1. Systematic Review:** Effective strategies to recruit adults with mild cognitive impairment (MCI) into nonpharmacological intervention trials are not well documented. Challenges to recruitment of adults with MCI into such trials include: stringent eligibility criteria; significant time investment required for participation; severity of the participant's cognitive impairment, which impacts adherence to the intervention; and mild impairments that are not routinely identified or diagnosed in the primary care setting, making it difficult to recruit adults with MCI.
- 2. Interpretation:** Mass mailing of age- and geo-targeted infographic postcards and brochures was the most effective approach for recruitment of adults with MCI into EXERT, an 18-month randomized controlled trial examining the effects of aerobic exercise on cognitive trajectory.
- 3. Future Directions:** Future trials should consider using age- and geo-targeted mass mailings to recruit adults with MCI. Trialists are encouraged to disseminate their recruitment experiences to inform optimal approaches supporting successful enrollment of adults with MCI into clinical trials.

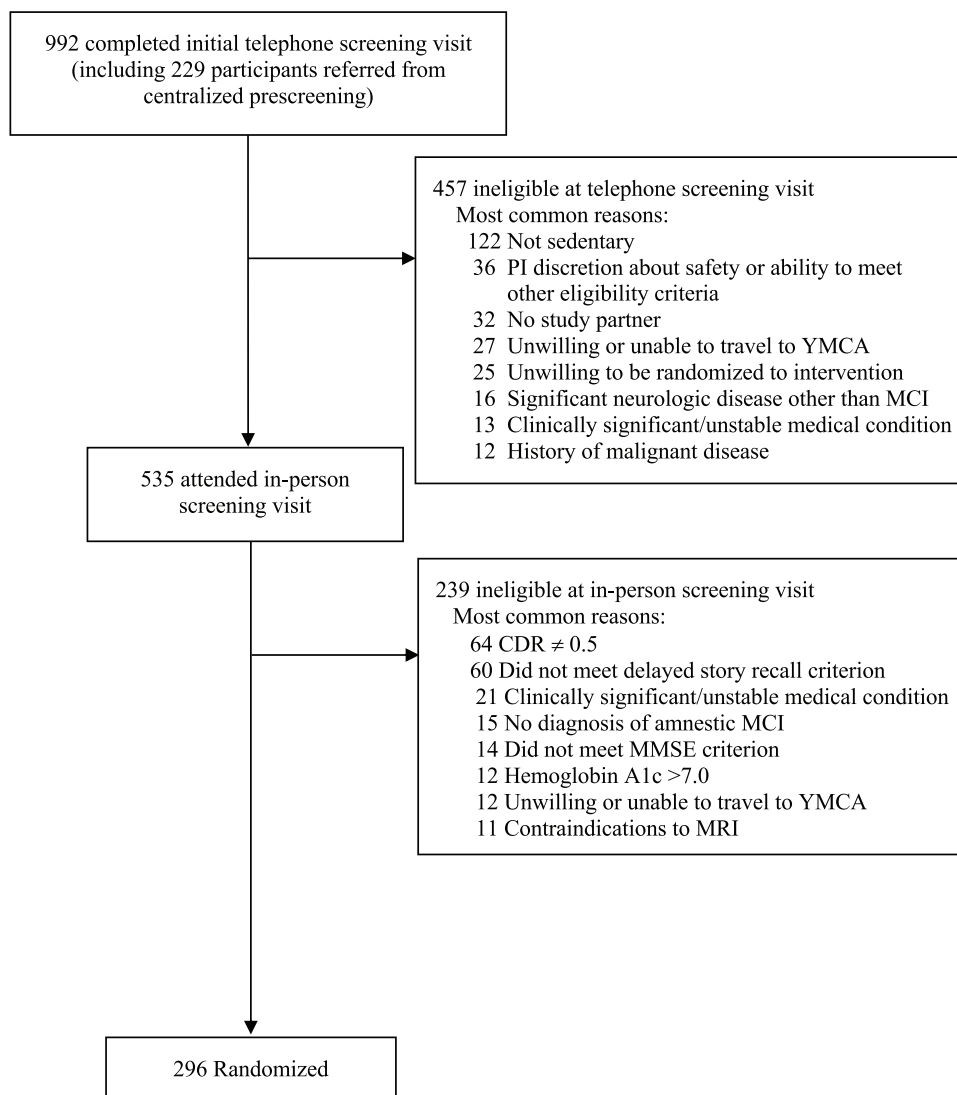
### HIGHLIGHTS

- Effective strategies to recruit adults with mild cognitive impairment (MCI) into trials are not established.
- EXERT is an 18-month multisite randomized controlled trial of aerobic exercise in adults with amnesic MCI.
- Age- and geo-targeted mass mailings of infographics recruited 52% of participants.
- Twenty-five percent of participants were recruited from memory clinics, registries, and electronic health records.
- Other recruitment sources were news media, local advertising, and community presentations.

bility at this visit included: (1) cognitive status: (a) CDR > 0.5 (4.7%); (b) CDR = 0 (22.1%); and (c) delayed verbal recall score exceeded threshold for inclusion (25.1%); (2) unstable medical condition (8.8%); and (3) no diagnosis of aMCI (6.3%). Primary reasons for ineligibility across screening visits did not differ by race, ethnicity, or education level (Tables S1-S3 in supporting information). Overall, 29.8% of telephone-screened individuals (296/992) and 55.3% of in-person screened individuals (296/535) were randomized into EXERT.

### 3.2 | Recruitment methods and randomization rates

Sites varied in the overall percentage of participants who contributed to the randomized cohort (range: N = 5 [1.7%] to N = 47 [15.9%]).



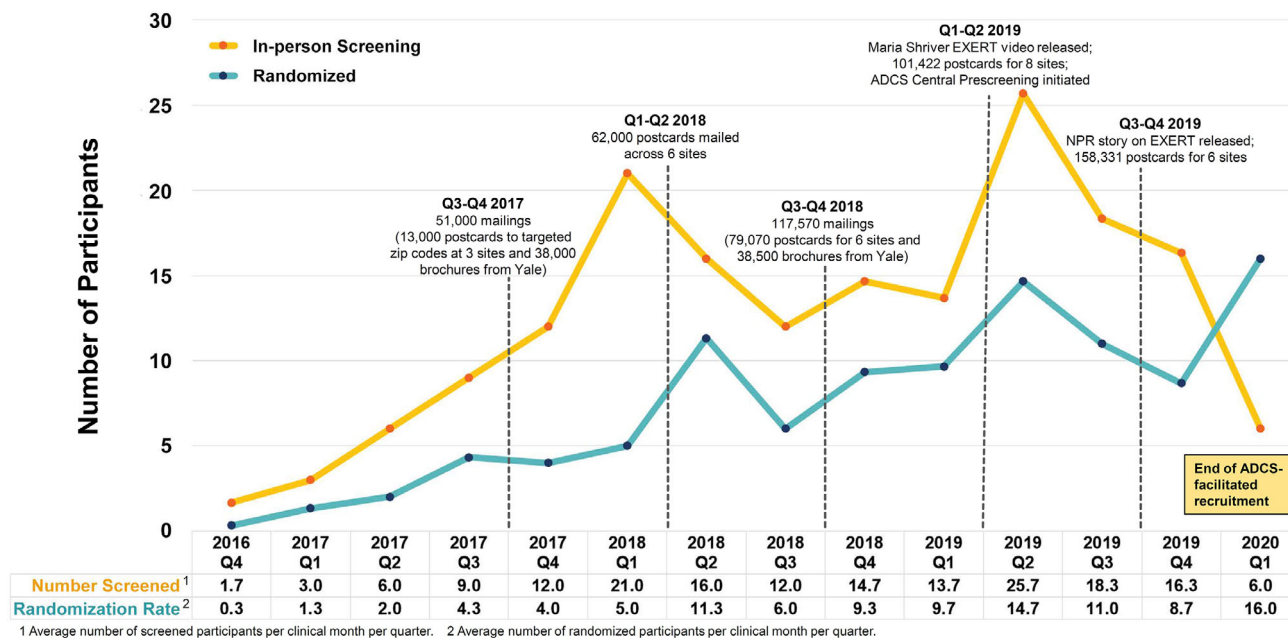
**FIGURE 1** EXERT study flow diagram. CDR, Clinical Dementia Rating; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging

Figure 2 shows the timeline of recruitment activities and randomization rates, defined as the mean number of participants randomized per active clinic month per quarter. Randomization rates in Quarter 4 of 2016 through Quarter 2 of 2017 were low when recruitment relied primarily on memory clinic patient rosters, patient registries, electronic health records, and community presentations. After the mailing of 51,000 age- and geo-targeted postcards and brochures, the randomization rate increased 2-fold to 4.3 and 4.0 randomizations per month in Quarters 3 and 4 of 2017, respectively.

In Quarters 1 and 2 of 2018, an additional 62,000 infographic postcards and brochures were mailed, which led to an increase of 163% in the randomization rate from 4.3 to 11.3 randomizations per month. The randomization rate in Quarter 4 of 2018 was 9.3 per month in response to an additional mailing of 117,570 infographic recruitment materials. In Quarter 2 of 2019, randomizations further increased to 14.7 per month after the release of the PSA, mailing of 101,422 infographic postcards, and initiation of a call center for centralized prescreening.

In Quarters 3 and 4 of 2019, the NPR story was released, centralized prescreening continued, and an additional 158,331 infographic postcards were mailed. In response, randomization peaked in Quarter 1 of 2020 at 16 randomizations per month, and the enrollment target was reached.

High initial screen failure rates were largely due to difficulties in recruiting individuals with an established clinical diagnosis of MCI who also met rigorous criteria for “sedentary,” which led to protocol revisions in Quarter 4 of 2017. Although it is well established that most individuals with aMCI in the community are undiagnosed,<sup>17</sup> some sites chose to recruit only individuals with a prior diagnosis of MCI. This practice excluded candidates who met all eligibility criteria but were unwilling or unable to obtain medical attention for a mild memory impairment. Thus, the protocol language was revised to indicate that a prior clinical diagnosis of aMCI, as defined by NIA/Alzheimer’s Association guidelines, was not required for eligibility. In addition, under the revised protocol, self-report of strength training (e.g., lifting weights)



**FIGURE 2** EXERT recruitment activity timeline. ADCS, Alzheimer's Disease Cooperative Study; NPR, National Public Radio

was not exclusionary when assessing sedentary status, because the focus of EXERT was to specifically examine the effects of aerobic exercise on cognition. These protocol modifications decreased the screen failure rate from 53.6% to 45.2% through August 2018. At that time, the protocol was further modified to remove the requirement for Logical Memory and Auditory Verbal Learning Test scores that fell at or below a specified cutpoint. With this modification, cognitive eligibility was confirmed with a global CDR of 0.5 and a memory component score of at least 0.5, and neuropsychological test performance and clinical assessments consistent with aMCI as per the site PI or study clinician. Simulation analyses were completed to confirm that the trial maintained sufficient power if individuals with milder MCI were recruited under the revised protocol. This last modification further reduced the screen failure rate to 37.3% from August 2018 through the end of recruitment. Individuals recruited under the revised protocol were similar in most characteristics but were more likely to be younger, to be women, and to have on average approximately one point higher MMSE scores relative to those recruited under the original protocol (Table S4 in supporting information).

### 3.3 | Sources of recruitment

Age- and geo-targeted infographic postcards and brochures were used to recruit more than half (52%) of randomized participants (Figure 3). Overall, 53.9% of White, 34.5% of Black/African American, 42.9% of Asian, 100% of Native American, and 66.7% of Hispanic/Latinx participants were recruited using this strategy. The total cost for this investment was \$221,612, or \$1439 per randomized participant, which takes into consideration payments to the vendor for mass mailings, print and shipping expenses at two clinical sites to manage local mass mailings, and staff time.

Twenty-five percent of participants were recruited from memory clinic patient rosters, patient registries, or electronic health records. The remainder learned about EXERT through word-of-mouth (6.1%), community educational presentations (5.4%), news media (1.7%), local (paid) advertising (5.4%), and other sources (e.g., Alzheimer's Association, primary care provider; 4.4%). Individuals recruited from postcards or brochures relative to those recruited from memory clinics, registries, and electronic health records had slightly higher average MMSE scores (28.3 vs. 27.4) but did not significantly differ on other characteristics (Table S5 in supporting information).

### 3.4 | Characteristics of randomized participants

Characteristics of randomized participants are provided in Table 1. Mean age was 74.5 (standard deviation [SD] 6.0) years. Education level was distributed as follows: 8.8% (0–12 years); 23.3% (13–15 years); and 67.9% (16 or more years). Overall, 78.0% were retired, and 96.6% reported independent living. There were 13.2% from underrepresented groups, including 9.8% Black/African American, 2.4% Asian, 1% Native American, and 1% Hispanic/Latinx. Mean MMSE was 28.0 (SD 1.9).

## 4 | DISCUSSION

### 4.1 | Summary

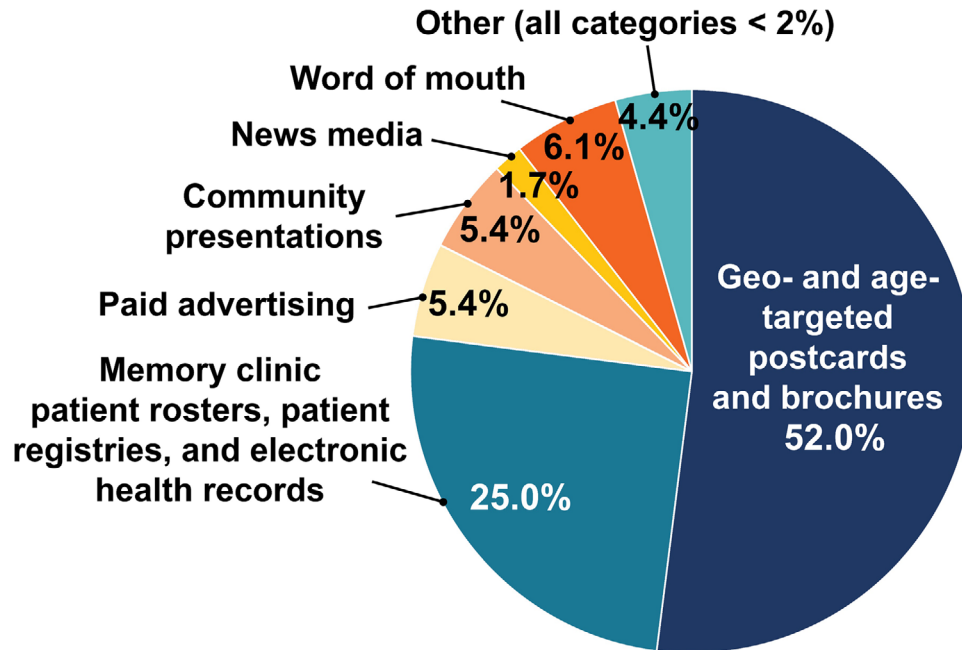
Recruitment into EXERT, an 18-month exercise trial among sedentary adults with aMCI, achieved its enrollment target. We faced multiple recruitment challenges related to inclusion criteria (e.g., sedentary, clinical diagnosis of MCI), intervention delivery (e.g., travel to YMCA), and willingness to commit to an intervention requiring significant

**TABLE 1** Baseline characteristics by sex among participants randomized into EXERT

	Total (N = 296)	Men (N = 127)	Women (N = 169)
Age, years, mean (SD)	74.5 (6.0)	75.6 (6.1)	73.6 (5.7)
Race, n (%)			
White	256 (86.5)	117 (92.1)	139 (82.2)
Persons of color	39 (13.2)	10 (7.9)	29 (17.2)
Native American	3 (1.0)	1 (0.8)	2 (1.2)
Asian	7 (2.4)	5 (3.9)	2 (1.2)
Black/African American	29 (9.8)	4 (3.1)	25 (14.8)
Other	1 (0.3)	0	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latinx	3 (1.0)	1 (0.8)	2 (1.2)
Not Hispanic or Latinx	287 (97.0)	122 (96.1)	165 (97.6)
Unknown or not reported	6 (2.0)	4 (3.1)	2 (1.2)
Education, years, mean (SD)	16.2 (2.4)	16.8 (2.3)	15.9 (2.3)
Education, years, n (%)			
0–12	26 (8.8)	7 (5.5)	19 (11.2)
12–15	69 (23.3)	19 (15.0)	50 (29.6)
16+	201 (67.9)	101 (79.5)	100 (59.2)
Marital status, n (%)			
Married	185 (62.5)	112 (88.2)	73 (43.2)
Widowed	33 (11.1)	3 (2.4)	30 (17.8)
Divorced	63 (21.3)	9 (7.1)	54 (32.0)
Never married	13 (4.4)	2 (1.6)	11 (6.5)
Unknown/other	2 (0.7)	1 (0.8)	1 (0.6)
Retired, n (%)	231 (78.0)	98 (77.2)	133 (78.7)
Type of residence, n (%)			
Independent living (house, apartment, or retirement community)	286 (96.6)	125 (98.4)	161 (95.3)
Lives with family	7 (2.4)	2 (1.6)	5 (3.0)
Senior residence	3 (1.0)	0	3 (1.8)
Body mass index, n (%)			
Normal (18.5–24.9 kg/m <sup>2</sup> )	76 (25.7)	26 (20.5)	50 (29.6)
Overweight (25.0–29.9 kg/m <sup>2</sup> )	103 (34.8)	50 (39.4)	53 (31.4)
Obese (≥30 kg/m <sup>2</sup> )	116 (39.2)	50 (39.4)	66 (39.1)
Unknown	1 (0.3)	1 (0.8)	0
Systolic blood pressure, n (%)			
< 120 mmHg	40 (13.5)	17 (13.4)	23 (13.6)
120–129 mmHg	58 (19.6)	23 (18.1)	35 (20.7)
130–139 mmHg	80 (27.0)	31 (24.4)	49 (29.0)
≥140 mmHg	118 (39.9)	56 (44.1)	62 (36.7)
Diastolic blood pressure, n (%)			
< 80 mmHg	181 (61.1)	76 (59.8)	105 (62.1)
80–89 mmHg	84 (28.4)	37 (29.1)	47 (27.8)
≥90 mmHg	31 (10.5)	14 (11.0)	17 (10.1)
MMSE score, mean (SD)	28.0 (1.9)	27.6 (2.0)	28.3 (1.7)

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.





**FIGURE 3** EXERT recruitment by source among 296 randomized participants

participant investment. There were several strategies that led to the trial's eventual recruitment success. Age- and geo-targeted infographic postcard and brochure mass mailings accounted for more than half of randomized participants. Outreach to memory clinic patients and existing patient registries and review of electronic health records accounted for 25% of those recruited, with earned media, advertisements, and community presentations accounting for the remainder. Strategic protocol modifications were important to respond to unforeseen recruitment obstacles that effectively widened the door to enrollment for candidates without a prior clinical diagnosis of aMCI, which likely will improve generalizability of EXERT findings to a larger number of adults with undiagnosed cognitive impairment.

## 4.2 | Challenges with recruitment

EXERT required that participants travel to a local YMCA four times per week for 18 months. This challenge may be especially potent for adults living with hallmark impairments in planning and organization (e.g., arranging the day's schedule to include exercise at the YMCA), reduced ability to take initiative (e.g., problem-solving challenges to exercise adherence when encountered), and impairments in short-term memory (e.g., remembering the appointment with the YMCA trainer).

NeuroExercise, a multicenter randomized controlled trial (RCT) of a 12-month aerobic exercise intervention in sedentary adults with aMCI, reported greater success recruiting participants from the community (62.1%) than clinics (37.9%).<sup>2</sup> NeuroExercise screened 1528 individuals over 18 months, including 835 (54.6%) deemed ineligible at screening.<sup>2,18</sup> In another 12-month RCT of home-based aerobic exercise in adults with aMCI, a total of 1620 individuals were screened, including 1550 (95.7%) who did not meet eligibility criteria

over a 4-year recruitment period.<sup>19</sup> EXERT experienced greater recruitment success, with screen failure rates of 46.1% and 44.7% after telephone and in-person screening visits, respectively, during 3.5 years of recruitment. EXERT partnered with a community-based organization for intervention delivery to test a model that could be sustainably deployed in the community if trial results are positive. Although there were challenges related to participant travel, the social component of the YMCA model may have been an important factor to help overcome this barrier. Reported recruitment barriers in NeuroExercise included trial duration and difficulties in transportation to the intervention site.<sup>2</sup> In EXERT, participants were recruited from areas near participating YMCAs to reduce transportation-related burden. At some sites, no-cost YMCA memberships were made available to a family member who could provide transportation.

Recruitment of participants meeting study criteria for sedentary status was a challenge. Recruitment efforts frequently attracted regular exercisers, given the resources that were promised to eligible participants (i.e., YMCA membership, a trainer). Our recruitment messaging was iteratively modified to discourage regular exercisers and attract those who were willing and able to invest in the study for personal or philanthropic reasons. In EXERT, although a validated structured interview was used to assess sedentary status, it is well known that self-reported physical activity is frequently overestimated. Although the interview is designed to obtain more reliable information, overestimation may have excluded some otherwise eligible study candidates.

## 4.3 | Recruitment from the community

Adults recruited from memory clinics tend to have more advanced cognitive impairment due to AD with more severe symptoms, whereas



adults recruited from the community tend to have earlier stage MCI with heterogeneous etiology.<sup>5</sup> Patients with earlier stage MCI are less likely to seek medical care for a cognitive impairment, which keeps them “under the radar” for a clinical diagnosis, thereby increasing the challenge of identifying these individuals for clinical trials.<sup>17</sup> A community-based approach to recruitment focused on identifying adults with subjective memory concerns, which can be indicative of MCI,<sup>20</sup> has the potential to engage study candidates with milder memory impairments who may not have previously sought out or received appropriate medical attention for this condition. For trials focused on prevention of cognitive decline, timing of the intervention is key.<sup>21</sup> If the goal is to prevent progression of MCI to dementia, participants in the earliest stages of MCI must be prioritized for enrollment. Reliance on memory clinics, patient registries, or medical records for study candidates may reduce the window of opportunity for prevention, given that these individuals are typically further along in the disease process. In EXERT, the “cast a wide net” approach for recruitment attracted many individuals without a prior clinical diagnosis of MCI but with a screening-verified cognitive impairment (e.g., global and memory CDR = 0.5).

#### 4.4 | Mass mailings

Mailing lists are frequently used to support recruitment of adults into AD prevention trials and registries, with varying success.<sup>22–25</sup> The Ginkgo Evaluation of Memory Study for cognitively normal older adults mailed ≈243,000 study brochures and followed up with ≈12,000, enrolling 25.2% of those screened.<sup>25</sup> Direct mailings have also been used to recruit cognitively impaired older adults into observational studies.<sup>23,26</sup> Lessons learned in EXERT show that culturally sensitive age- and geo-targeted mass mailings can be a useful tool in the recruitment arsenal but must be continuously evaluated for effectiveness.

In EXERT, mean education level of enrollees was 16.2 years, similar to another recent exercise trial in adults with aMCI.<sup>19</sup> Mean educational level in EXERT is similar to the MCI cohort of the Baltimore Longitudinal Study of Aging and slightly higher than the MCI cohort of the Einstein Aging Study.<sup>27,28</sup> Despite strategic messaging and outreach through mailings, EXERT recruitment strategies were successful in recruiting <10% with 12 or less years of education and 32% with <15 years. Future trials should develop strategic plans and an appropriate budget for vigorous grassroots engagement at the local level to reach more diverse communities.

#### 4.5 | Alignment with NIA National Strategy for Recruitment

EXERT recruitment strategies were responsive to the major themes of the NIA's *National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias (ADRD) Clinical Research*.<sup>29</sup>

#### 4.5.1 | Increase awareness and engagement

EXERT's multifaceted recruitment strategy addressed the Strategy's recommendations to identify appropriate audiences using age- and geo-targeted mailings, frame outreach and recruitment messaging around brain health rather than disease, use focus groups to hone recruitment material content and impact, implement many outreach strategies in parallel, and use key influencers for message delivery (e.g., Maria Shriver).

#### 4.5.2 | Build and improve research infrastructure

ADCS provided a solid infrastructure for EXERT to support efficient recruitment and trial conduct through centralized management of clinic activities, prescreening, and intervention delivery.

#### 4.5.3 | Engage local communities and support participants

Sites provided educational presentations to the community about the importance of exercise on brain health and partnered with local organizations and other stakeholders to promote the trial, particularly those representing underserved minority groups. Historically, clinical trials have not included adequate minority representation, with Hispanics and African Americans representing 18.5% and 13.4% (respectively) of the US population but only 5% of clinical trial participants.<sup>30,31</sup> We made a concerted effort to recruit racial and ethnic minorities into EXERT (13.2% of randomized participants) by developing culturally appropriate and sensitive multi-media messaging (print, radio, TV), geo-targeting areas in mailings with higher demographic diversity, and prioritizing these individuals for scheduling of screening and clinic appointments. We also critically examined eligibility criteria to identify potential biases that could exclude some groups, which motivated, in part, elimination of the requirement for a prior clinical diagnosis of MCI. This revision also opened up enrollment to those who had not previously sought out or received a diagnosis for various reasons (e.g., individual: financial, access to health care, cultural issues, disinterest/fear; provider: conservative diagnosis practices, inexperience).

#### 4.5.4 | Develop an applied science of recruitment

The focus of this article is to summarize and disseminate the most effective recruitment strategies for community-based lifestyle interventions in adults with MCI. In EXERT, we critically examined each recruitment tactic to assess its potential impact on the receiver (i.e., using focus groups) and on recruitment (i.e., by tracking response rate) over time to monitor progress and ensure successful recruitment. Many MCI and ADRD trials take far more time to recruit than planned, which delays scientific progress. When screen fail rates are high, it is

imperative that restrictive entry criteria be re-examined to determine whether they can be relaxed without affecting the integrity of the trial. In EXERT, these adaptive and responsive changes were fundamental to reaching our recruitment goal.

We also tracked recruitment costs associated with mass mailings to inform future trials. Mass mailings in EXERT cost \$221,612, or \$1439 per randomized participant. We recommend that realistic costs for successful recruitments be incorporated into trial budgets and that funding agencies prioritize thoughtful and strategic investment in recruitment to support successful completion of ADRD trials.

## 5 | CONCLUSION

Recruitment into EXERT, an 18-month exercise trial in sedentary older adults with aMCI, was challenging but ultimately successful due to our deployment of a multifaceted recruitment strategy. Our findings suggest that the recruitment approach in lifestyle intervention trials needs to be iteratively responsive and adaptive to develop new strategies when others fail. The redeployment of central resources from ADCS to develop and manage study-wide mass mailings and media campaigns was instrumental to the successful completion of recruitment for EXERT. The initial reliance on sites for all recruitment activity for the trial led to slow rates of enrollment for most sites that relied on memory clinic rosters, registries, and sporadic local outreach activities. Overall, our results demonstrate that use of age- and geo-targeted mass mailings was the most effective approach to recruitment of a diverse cohort of older adults with aMCI into EXERT and should be considered in recruitment planning for future lifestyle and other nonpharmacological intervention trials.

## ACKNOWLEDGMENTS

The EXERT trial is supported by the Alzheimer's Disease Cooperative Study (NIH/NIA U19 AG010483; Principal Investigator: Howard Feldman, MDCM; EXERT Project Directors: Laura D. Baker, PhD and Carl W. Cotman, PhD). Intervention delivery was overseen by Wake Forest School of Medicine: Jeffrey Katula, PhD; Elizabeth Chmelo, MS; Barbara Nicklas, PhD; and Cara Johnson, MA, in partnership with the national YMCA of America: Heather Hodge, MEd; Valerie Lawson, MS RD. The following institutions and site Principal Investigators participated in EXERT: Cleveland Clinic Lou Ruvo Center for Brain Health: Marwan Sabbagh, MD; Charles Bernick, MD, MPH; Duke University Medical Center: Kathleen Welsh-Bohmer, PhD; Emory University: Whitney Wharton, PhD; Joseph Nocera, PhD; Great Lakes Clinical Trials: Steve Satek, MBA; Jeffrey Ross, MD; Linda Rice, PhD; Kansas University, Kansas City: Jeffrey Burns, MD, MS; Mt. Sinai School of Medicine: Clara Li, PhD; Mary Sano, PhD; New York University Medical Center: Martin Sadowski, MD, PhD; Steven Ferris, PhD; Stanford University School of Medicine: J. Kaci Fairchild, PhD; Jerome Yesavage, MD; University of California, Irvine: Steven Tam, MD; University of Kentucky, Lexington: Allison Caban-Holt, PhD; Shoshana Bardach, PhD; University of North Texas Health Science Center: Sid O'Bryant, PhD; Leigh Johnson, PhD; University of Wisconsin-Madison School of

Medicine: Ozioma Okonkwo, PhD; Wake Forest School of Medicine: Laura Baker, PhD; Yale University School of Medicine: Christopher Van Dyck, MD. EXERT Coordinating Center Lead Project Managers are Rosemary Morrison, MPH, and Sean Kipperman.

## CONFLICTS OF INTEREST

AHS, AZL, OCO, SPT, JFK, GM, DB, AAS, KAS, RHM, SAK, JM, DT, RGT, CWC, and LDB have no conflicts of interest. HHF reports UCSD service agreements for consulting with Axon Neuroscience, Banner Health, Roche/Genentech (DMC and DSMB), Samus Therapeutics, Tau Consortium, Novo Nordisk, and Janssen; ADCS Clinical Trials grant funding from Annovis (Posiphen), Biohaven (BH 4157), Vivoryon (PQ 912), AC Immune (ACI-24-1301), LuMind (ADC-059-LIFE-DSR); and Research funding from NIA/NIH (U19 AG010483, P30 AG062429, R01 AG061146-01, 1R56AG069130-01, R01 AG051618), CIHR (137794, 254450, 294127), Brain Canada (4469), and Alzheimer's Association (SG-20-690388-PEACE AD). KWB reports grants from VeraSci Inc. and personal fees from Biogen. CVD reports consulting fees from Roche and Eisai and grants for clinical trials from Biogen, Roche, Eisai, Eli Lilly, Genentech, Janssen, Novartis, Biohaven, and Merck.

## ORCID

Aladdin H. Shadyab  <https://orcid.org/0000-0002-9693-0522>

## REFERENCES

1. Locke DEC, Greenaway MC, Duncan N, et al. A patient-centered analysis of enrollment and retention in a randomized behavioral trial of two cognitive rehabilitation interventions for mild cognitive impairment. *J Prev Alzheimers Dis*. 2014;1(3):143-150.
2. Sanders ML, Stuckenschneider T, Devenney KE, et al. Real world recruiting of older subjects with mild cognitive impairment for exercise trials: community readiness is pivotal. *J Alzheimers Dis*. 2018;62(2):579-581.
3. Smith G, Chandler M, Locke DEC, et al. Behavioral interventions to prevent or delay dementia: protocol for a randomized comparative effectiveness study. *JMIR Res Protoc*. 2017;6(11):e223.
4. Rodakowski J, Goliass KW, Reynolds CF, et al. Preventing disability in older adults with mild cognitive impairment: a strategy training intervention study. *Contemp Clin Trials Commun*. 2019;15:100368.
5. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 2014;275(3):214-228.
6. Lam LC, Chan WC, Leung T, Fung AW, Leung EM. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. *PLoS One*. 2015;10(3):e0118173.
7. Amofa PA Sr, DeFeis B, De Wit L, et al. Functional ability is associated with higher adherence to behavioral interventions in mild cognitive impairment. *Clin Neuropsychol*. 2020;34(5):937-955.
8. Iliffe S, Robinson L, Brayne C, et al. Primary care and dementia: 1. diagnosis, screening and disclosure. *Int J Geriatr Psychiatry*. 2009;24(9):895-901.
9. Folstein MF, Folstein SE, McHugh PR. Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
10. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140(6):566-572.

11. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol*. 1980;7(5):486-488.
12. Mayer CJ, Steinman L, Williams B, Topolski TD, LoGerfo J. Developing a telephone assessment of physical activity (TAPA) questionnaire for older adults. *Prev Chronic Dis*. 2008;5(1):A24.
13. O'Bryant S. For Alzheimer's disease, we can put some hope in an Rx for exercise. *Fort Worth Star Telegram*. January 6, 2017. Available at <https://www.star-telegram.com/opinion/opn-columns-blogs/other-voices/article125029024.html>. Accessed November 25, 2020.
14. Proctor K, World class research in our hometown: Sticht Center for Healthy Aging & Alzheimer's Prevention works to help keep older adults strong, healthy and engaged. August 14, 2018. Available at [https://journalnow.com/archive/world-class-research-in-our-hometown-sticht-center-for-healthy-aging-alzheimer-s-prevention-works/article\\_70200c26-9ff4-11e8-a2b6-dbeda8bce568.html](https://journalnow.com/archive/world-class-research-in-our-hometown-sticht-center-for-healthy-aging-alzheimer-s-prevention-works/article_70200c26-9ff4-11e8-a2b6-dbeda8bce568.html). Accessed November 25, 2020.
15. Dearing T, Potential new drug for Alzheimer's isn't a pill; it's exercise. September 18, 2017. Available at [https://www.nj.com/healthfit/2017/09/potential\\_new\\_drug\\_for\\_alzheimers\\_isnt\\_a\\_pill\\_its.html](https://www.nj.com/healthfit/2017/09/potential_new_drug_for_alzheimers_isnt_a_pill_its.html). Accessed November 25, 2020.
16. Hamilton J, "Is Aerobic Exercise the Right Prescription for Staving Off Alzheimer's?" National Public Radio. July 18, 2019. Available at <https://www.npr.org/sections/health-shots/2019/07/18/743189541/is-aerobic-exercise-the-right-prescription-for-staving-off-alzheimers>. Accessed November 25, 2020.
17. Sabbagh MN, Boada M, Borson S, et al. Early detection of mild cognitive impairment (MCI) in primary care. *J Prev Alzheimers Dis*. 2020;7(3):165-170.
18. Stuckenschneider T, Sanders ML, Devenney K, et al. NeuroExercise: the effect of a 12-month exercise intervention on cognition in mild cognitive impairment – a multicenter randomized controlled trial. *Front Aging Neurosci*. 2021;12:621947.
19. Tarumi T, Rossetti H, Thomas BP, et al. Exercise training in amnesic mild cognitive impairment: a one-year randomized controlled trial. *J Alzheimers Dis*. 2019;71(2):421-423.
20. van Harten AC, Mielke MM, Swenson-Dravis DM, et al. Subjective cognitive decline and risk of MCI: the mayo clinic study of aging. *Neurology*. 2018;91(4):e300-e312.
21. Sperling RA, Jack CR Jr, Aisen PS. Testing the right target and right drug at the right stage. *Sci Transl Med*. 2011;3(111):111cm33.
22. Gombosev A, Salazar CR, Hoang D, Cox CG, Gillen DL, Grill JJ. Direct mail recruitment to a potential participant registry. *Alzheimer Dis Assoc Disord*. 2019;10:1097.
23. Grill JD, Galvin JE. Facilitating Alzheimer disease research recruitment. *Alzheimer Dis Assoc Disord*. 2014;28(1):1-8.
24. Schneider LS. Recruitment methods for United States Alzheimer disease prevention trials. *J Nutr Health Aging*. 2012;16(4):331-335.
25. Fitzpatrick AL, Fried LP, Williamson J, et al. Recruitment of the elderly into a pharmacologic prevention trial: the ginkgo evaluation of memory study experience. *Contemp Clin Trials*. 2006;27(6):541-553.
26. Melikyan ZA, Greenia DE, Corrada MM, Hester MM, Kawas CH, Grill JD. Recruiting the oldest-old for clinical research. *Alzheimer Dis Assoc Disord*. 2019;33(2):160-162.
27. Grober E, Wang C, Kitner-Triolo M, et al. Prognostic value of learning and retention measures from the free and cued selective reminding test to identify incident mild cognitive impairment. *J Int Neuropsychol Soc*. 2021:1-8.
28. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. *Alzheimer Dis Assoc Disord*. 2012;26(4):335-343.
29. National Institute on Aging. Together we make the difference: national strategy for recruitment and participation in Alzheimer's and related dementias clinical research. 2018. Available at <https://www.nia.nih.gov/research/recruitment-strategy>. Accessed November 25, 2020.
30. United States Census Bureau. Population estimates. July 1, 2019. Available at <https://www.census.gov/quickfacts/fact/table/US/PST045219>. Accessed April 28, 2021.
31. Coakley M, Fadiran EO, Parrish LJ, et al. Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials. *J Womens Health (Larchmt)*. 2012;21(7):713-716.

## SUPPORTING INFORMATION

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

**How to cite this article:** Shadyab AH, LaCroix AZ, Feldman HH, et al. Recruitment of a multi-site randomized controlled trial of aerobic exercise for older adults with amnesic mild cognitive impairment: The EXERT trial. *Alzheimer's Dement*. 2021;17:1808–1817. <https://doi.org/10.1002/alz.12401>