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Short Communication

Eligibility for donanemab trial in a population-based study of cognitive aging

Katherine E. Jones[a,b], Jeremiah A. Aakre[c], Anna M. Castillo[c], Vijay K. Ramanan[a], Walter K. Kremers[c], Clifford R. Jack Jr[d], Prashanthi Vemuri[d], Christopher G Schwarz[d], Val J. Lowe[d], David S. Knopman[a], Ronald C. Petersen[a], Jonathan Graff-Radford[a,1], Maria Vassilaki[c,1,*]

[a] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[b] Wake Forest University, Winston-Salem, NC, USA
[c] Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA
[d] Department of Radiology, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

The study aimed to assess eligibility for donanemab phase 3 trial in participants of the Mayo Clinic Study of Aging with mild cognitive impairment (MCI) or mild dementia consistent with Alzheimer's disease (AD) clinical syndrome, positive brain amyloid burden, and available tau PET. There were 817 study participants, 60–85 years old, with MCI or dementia consistent with AD clinical syndrome. Applying the Mini-Mental State Examination criteria (20 to 28) and excluding participants with imaging contraindications reduced the sample to 769; 275 participants had amyloid PET available, of whom 130 had also tau PET at the same visit; 56 participants were amyloid positive, had tau PET available at the same visit, and of those, 27 had evidence of tau pathology measured by 18F-flortaucipir PET imaging. Additional eligibility criteria reduced the eligible participants to 23 % (13 out of 56 participants). Neuroimaging findings, central nervous system exclusions, and history of malignancy were the major exclusions.

1. Introduction

Alzheimer's Disease (AD) is the most common type of dementia, comprising 60–80 % of dementia cases [1]. The number of people living with dementia is projected to triple by the year 2050, impacting the individual patient and their family, with extended societal costs [2]. The development of anti-beta amyloid monoclonal antibodies (mAbs) —such as aducanumab, lecanemab, and most recently, donanemab—has shown potential to slow disease progression in patients in the early stages of biomarker-confirmed symptomatic AD.

Previous studies on aducanumab and lecanemab assessed patient eligibility in variable study settings [3,4], adopting the clinical trial eligibility criteria, or assessing eligibility based on the U.S. Food and Drug Administration (FDA) -approved prescribing information on lecanemab [5], suggesting that the fraction of patients eligible for these treatments would be small, with most patients excluded due to age, chronic conditions, laboratory or neuroimaging findings. The FDA has recently approved the use of donanemab for the treatment of early-stage symptomatic AD (i.e., patients with amyloid-positive mild cognitive impairment or mild dementia) [6].

AD is characterized by the accumulation of both amyloid and tau pathology, i.e., amyloid plaques and neurofibrillary tangles [7]. Tau accumulation is more proximal than amyloid accumulation to clinical symptoms, while the amount and anatomic location of tau accumulation are important for the type and severity of clinical symptoms [8,9]. In the donanemab trial [10], tau PET positivity was an additional inclusion criterion; the trial required the participants to have evidence of tau accumulation in the brain that was enough (in the medial temporal lobe) to ascertain AD and that the disease could progress during the trial period [8]. The present study aimed to assess eligibility for donanemab by applying the donanemab phase 3 clinical trial eligibility criteria [10] to participants in the Mayo Clinic Study of Aging with MCI or mild dementia consistent with AD clinical syndrome, positive brain amyloid burden, and available tau PET. The study hypothesized that a small proportion of early-stage symptomatic biomarker-confirmed AD participants would be eligible for the trial.

* Corresponding author at: Department of Quantitative Health Sciences, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail address: vassilaki.maria@mayo.edu (M. Vassilaki).
[1] Equal contributors.

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2. Methods

2.1. Study population

The Mayo Clinic Study of Aging (MCSA) [11] is a population-based cohort study that examines the epidemiology, risk factors, and biomarkers of mild cognitive impairment (MCI) and dementia in older adults living in Olmsted County. Details of the study have been reported previously [11]. Briefly, participants are randomly selected community-dwelling older adults using the Rochester Epidemiology Project (REP) [12] medical records linkage system resources. When the study was established in 2004, 70–89-year-olds were invited to participate. The study population was expanded in 2012 to include individuals ages 50–69.

At baseline, a study coordinator conducted a risk factor assessment; participants answered questions regarding their personal and family medical history, medications, and neuropsychiatric symptoms. The Clinical Dementia Rating (CDR) scale was administered to the study partner for the majority of participants [13]. A physician reviewed the participant's medical history and administered a neurological examination and the Short Test of Mental Status, from which the Mini-Mental State Examination (MMSE) score can also be derived [14]. In addition, nine neuropsychological tests were administered by a psychometrist to assess cognitive performance in four domains, i.e., memory, language, attention/executive, and visuospatial [11].

Following each MCSA visit, the participant's final diagnosis (cognitively unimpaired (CU), MCI, dementia) was determined by consensus by a panel including the study coordinator, the physician, and a neuropsychologist after reviewing the data. All evaluators were blind to previous diagnoses. Based on the participant's evaluation, they were determined to be cognitively unimpaired (CU), to have mild cognitive impairment (MCI) [15], or dementia [16–18] based on published criteria. Apolipoprotein E (APOE) $\varepsilon 4$ status was determined from a blood draw at MCSA baseline assessment. Participants were defined as *APOE* $\varepsilon 4$ carriers or non-carriers if they had at least one $\varepsilon 4$ allele or none, respectively. In addition, expert RN abstractors reviewed the participants' medical records to assess comorbidities.

2.2. Standard protocol approvals, registrations, and patient consent

Study approval was obtained from the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota. Participants provided written informed consent before participation. In the case of participants with cognitive impairment sufficient to interfere with capacity, assent was obtained from a legally authorized representative.

2.3. Neuroimaging biomarkers

Neuroimaging biomarker acquisition has been presented previously in more detail [19,20]. MRI imaging was acquired on 3T scanners (GE from 2009 to 2017 and Siemens from 2017 - present) and has been described in detail previously [19,21]. For the participants, T2-weighted FLAIR (fluid-attenuated inversion recovery)-MRI images were used for WMH segmentation [22], as described in detail previously [23]. As previously detailed [24], 3D MPRAGE and susceptibility-weighted imaging (SWI) were reviewed, and superficial siderosis was identified and classified. Cerebral microbleeds were quantified on 3-tesla MRI scans with T2* gradient recalled echo sequences and SWI based on published consensus criteria, [25] as previously published in detail [26].

Amyloid PET imaging was performed with ^{11}C-Pittsburgh Compound B (PIB) [27,28]. Tau PET imaging was performed using AV-1451 (18F-flortaucipir), synthesized on-site with a precursor supplied by Avid Radiopharmaceuticals [29]. Amyloid-PET and tau-PET standardized uptake value ratio (SUVR) values were formed by normalizing regions of interest to the cerebellar Crus grey matter [19]. The SUVR for amyloid was determined by normalizing prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate, and the precuneus to the cerebellar Crus gray matter, and amyloid positivity (*A*+) was defined for the current study as an SUVR value ≥37 centiloids [10]. Tau PET positivity was assessed visually for typical AD pattern, while mild, diffuse, or small, single focal sites of uptake were not considered typical of AD. Specifically, a negative AD tau pattern consisted of no increased neocortical activity or increased neocortical activity isolated to the mesial temporal, anterolateral temporal, and/or frontal regions. A positive AD tau pattern showed increased neocortical activity in the posterolateral temporal, occipital, parietal, posterior cingulate or precuneus regions or increased activity in the frontal region accompanied by increases in the prior regions. The participants' MRI scans were used to localize the regions used to quantify the PET images. PET data were not corrected for partial volume. We used the time of the amyloid and tau PET as the study baseline.

2.4. Statistical analysis

Descriptive statistics (mean, standard deviation [SD], median, first and third quartile, count, percentage) were used to summarize participants' characteristics. Details on the eligibility criteria used are provided in the Supplemental Materials Appendix. All analyses were performed using the SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

3. Results

There were 4188 community dwelling MCSA participants aged 60–85 years (mean (SD) age was 73 (8) years at first visit on or after 1/1/2009; 51 % were male) with a visit on or after 1/1/2009 (year of PiB PET introduction). Eight hundred seventeen participants had MCI ($n = 782$) or dementia ($n = 35$) consistent with Alzheimer's disease (AD) clinical syndrome, of whom 782 had an MMSE 20–28 (Fig. 1, i.e., 35 participants were excluded due to the MMSE criterion; 24 participants with MCI and 11 with dementia). Thirteen participants had contraindications to MRI/PET, resulting in 769 participants with MCI/mild AD clinical syndrome. Thirty-six percent (275 of 769) had undergone amyloid PET (127 were amyloid positive (*A*+) for centiloid≥ 37), of whom 130 had both amyloid and tau PET scans available at the same visit. Forty-three percent (56 out of 130) participants had an amyloid positive scan (*A*+); we consider them the denominator for the donanemab eligibility fraction estimation. All 56 participants had an education of 11 or more years (range 11–20 years) and underwent neuropsychological testing providing valid data for their cognitive performance, fulfilling this eligibility criterion ("adequate literacy, vision, and hearing for neuropsychological testing")(10). MCSA requires a study partner, leaving a few participants without a partner; thus, we considered fulfilling this criterion for the donanemab trial, as well.

Twenty-seven of the 56 *A*+ participants were tau PET positive (*T*+) by visual inspection, and 29 *A*+ participants were T- (Table 1). Although Table 1 includes both *T*+ and T- participants, only *T*+ participants were eligible for the phase 3 donanemab trial. Applying the exclusion criteria shown in Table 1 reduced the eligible participants to 23 % (13 out of 56 *A*+ participants with available tau PET at the same visit) mainly due to neuroimaging findings, central nervous system exclusions [i.e., Parkinson's disease ($n = 1$), epilepsy ($n = 7$), coma/brain damage ($n = 3$), or intracranial injury ($n = 1$)], and history of malignancy (excluding benign tumors, basal cell carcinoma, squamous cell carcinoma, other non-melanoma skin cancers, localized prostate cancer or cancer of the lip). Although we did not exclude participants without a study partner, 10 of the 56 *A*+ participants did not report a study partner; all 10 participants had MCI. Five participants without a partner belonged to the *T*+ group (Table 1).

The study also assessed the trial exclusion criteria for the 127 participants who were 60 to 85 years of age with an MMSE score of 20

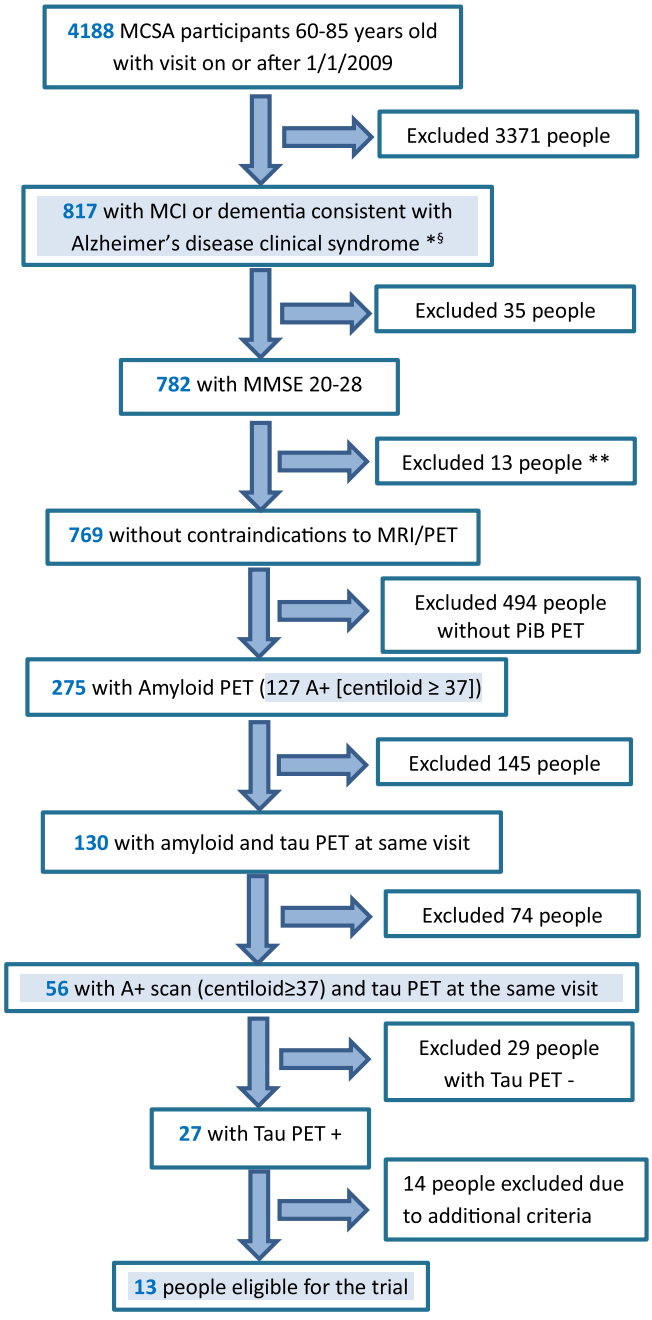

Fig. 1. Eligibility criteria for the donanemab trial.
*We excluded patients who were clinically diagnosed with the following: hard-to-classify dementia (1 person), vascular dementia via NINDS-AIREN criteria (2 people), Parkinson's disease (4 people), stroke (10 people), multiple infarctions (3 people), subarachnoid hemorrhage (1 person), subdural hematoma (1 person), alcohol use disorder (1 person), prior intellectual disability (1 person), and other metabolic or toxic disorder (1 person).
§We also verified that patients did not have these diagnoses at the clinical assessment: Lewy body dementia, frontotemporal dementia, intracerebral hemorrhage, drug-related psychiatric diagnosis, Binswanger's disease, progressive supranuclear palsy, and multiple sclerosis.
**Contraindications were: pacemaker (9 people), QTc score out of range (2 people), craniotomy (1 person), failed metal screening (1 person).

to 28 (inclusive) and had an amyloid positive PET scan (Fig. 1) without considering the tau PET availability. Forty-three percent (55 out of 127) of participants had no exclusions and, having also fulfilled the inclusion criteria (on age, having MCI/mild AD clinical syndrome, MMSE score, and *A*+ PET), would be eligible for the trial without considering the tau PET assessment (Table S1).

Finally, we compared the characteristics of participants with MCI/mild AD clinical syndrome, 60–85 years old, who chose to undergo amyloid PET (n = 275; Fig. 1) vs. those who did not choose to have an amyloid PET scan (n = 494; Fig. 1). Overall, participants without amyloid PET were, on average, older, with a higher frequency of three or more comorbidities (Table S2). Only 70 of the 494 participants without amyloid PET, had MRI available; thus, although we include neuroimaging findings available at the time of the amyloid PET, we do not provide a p-value for the differences in exclusions between the two groups. However, disregarding the neuroimaging findings, all other differences between the groups were not statistically significant except for autoimmune disorders in the past 1 year (p = 0.02).

4. Discussion

Applying the phase 3 donanemab trial eligibility criteria resulted in 23 % of the 56 *A*+ participants with available tau PET at the same visit, with MCI or mild dementia being eligible for the trial (60–85 years old with an MMSE score of 20–28). Neuroimaging findings, central nervous system exclusions, and a history of malignancy were the major exclusions. Present study findings agree with previous studies on the eligibility of anti-beta amyloid mAbs treatments [3–5,30–32], based on clinical trial operationalized eligibility criteria or FDA-approved prescribing information, in population-based or clinic-based settings or medicare beneficiaries, showing that a small fraction of individuals with biomarker-confirmed early symptomatic AD would qualify for anti-beta amyloid mAbs treatments.

A recent study(5) evaluating the eligibility of older adults (≥70 years old) to receive lecanemab treatment according to the FDA-approved prescribing information suggested that 6.2 % of adults 70 years or older would be eligible for lecanemab treatment, without including patients with factors suggesting increased risk for adverse events [(i.e., history of stroke, anticoagulant use, homozygote for APOE ε4, and neuroimaging findings (superficial siderosis, microbleeds (>4), lacunes, Fazekas score equal to 3 and signs of intracerebral hemorrhage)]. The Pittock et al. study [3], also based on the MCSA, including participants 50–90 years old, suggested that 8 % of participants with positive amyloid PET scan and early AD would be eligible to receive lecanemab treatment. This is a lower percentage than the one in the Dittrich et al. study [5], where 18 of 30 amyloid-positive participants with MCI or mild dementia were eligible for lecanemab treatment without any of the factors requiring additional consideration. However, this is not surprising, as the study by Pittock et al. used the stricter clinical trial eligibility criteria; when these eligibility criteria were relaxed to include all participants with MCI (instead of applying the additional clinical trial cognitive criteria), the percent eligibility more than doubled to 17.4 % of participants with MCI.

The present study is based on the MCSA, as was the Pittock et al. study(3), but the sampling strategy is different; the first study(3) selected community-dwelling adults with positive-amyloid PET first and then selected participants with MCI or dementia consistent with AD clinical syndrome and assessed the remaining eligibility criteria. The current study followed a different approach, closer to clinical practice; first, the participants with MCI or dementia consistent with AD clinical syndrome were selected, and then the remaining eligibility criteria, including amyloid and tau PET positivity, were assessed (Fig. 1). The phase 3 clinical trials for lecanemab and donanemab each had their unique eligibility criteria, even though there was some overlap (e.g., history of malignancy operationalized by us based on ICD-9/10 diagnoses codes), but even for such similar criteria, the time-period observed might have

Table 1
Characteristics of participants who met donanemab inclusion criteria, had a positive amyloid PET and an available tau PET at the same visit.

	Amyloid PET positive[¥]		
Characteristics	*T*+ (*N* = 27)	*T*- (*N* = 29)	Total (*N* = 56)
Age at study baseline, mean (SD)	78.1 (5.3)	79.4 (4.0)	78.7 (4.6)
Sex, female	18 (66.7 %)	10 (34.5 %)	28 (50.0 %)
APOE ε4 positive[*]	17 (70.8 %)	14 (51.9 %)	31 (60.8 %)
Education (years), mean (SD)	14.5 (2.6)	14.8 (2.6)	14.7 (2.6)
Cognitive Impairment			
Mild cognitive impairment	25 (92.6 %)	27 (93.1 %)	52 (92.9 %)
Dementia	2 (7.4 %)	2 (6.9 %)	4 (7.1 %)
MMSE from short test 20–28, mean (SD) [†]	25.6 (1.8)	26.2 (2.0)	25.9 (1.9)
Chronic conditions [‡]			
Two or more	20 (80.0 %)	22 (78.6 %)	42 (79.2 %)
Three or more	15 (60.0 %)	15 (53.6 %)	30 (56.6 %)
Total number of exclusions[∞], median (range)	1 (0–2)	1 (0–3)	1 (0–3)
No exclusions[§]	**13** (48.1 %)	10 (34.5 %)	23 (41.1 %)
Having one or more exclusions[§]	14 (51.9 %)	19 (65.5 %)	33 (58.9 %)
Exclusions considered[§]			
CNS-related exclusions[||]	9 (33.3 %)	12 (41.4 %)	21 (37.5 %)
Neuroimaging findings at the time of PET scan[*]	4 (14.8 %)	7 (25.0 %)	11 (20.0 %)
Greater than 4 micro-hemorrhages	2 (7.4 %)	4 (14.3 %)	6 (10.9 %)
Superficial Siderosis in 2+ regions	1 (3.7 %)	0 (0.0 %)	1 (1.8 %)
Severe WMH (90th% of CU/MCI cohort)	3 (11.1 %)	4 (13.8 %)	7 (12.5 %)
Non-CNS related exclusions			
Serious risk of suicide, past 1 year	0	0	0
Psychiatric hospitalization, past 6 months	1 (3.7 %)	0 (0.0 %)	1 (1.8 %)
Malignant neoplasms, past 5 years[£]	6 (22.2 %)	7 (24.1 %)	13 (23.2 %)
Alcohol or substance abuse, past 2 years	0 (0.0 %)	1 (3.4 %)	1 (1.8 %)
Liver impairment, past 6 months	0	1 (3.4 %)	1 (1.8 %)
End-stage renal disease, past 6 months	0 (0.0 %)	1 (3.4 %)	1 (1.8 %)
Autoimmune disorder, past 1 year[#]	0	0	0

Abbreviations: *T*+: tau PET positive by visual inspection; T-: tau PET negative by visual inspection; APOE=apolipoprotein E; CNS=Central nervous system; MMSE=Mini Mental State Examination; WMH=White Matter Hyperintensities; CU = cognitively unimpaired; MCI=mild cognitive impairment.
N(%) unless otherwise specified. Bold and highlighted present the number of eligible participants (13 of 56) for the donanemab phase 3 trial.

[¥] SUVR value ≥37 centiloids.

[*] 5 missing for APOE ε4 positive; 1 missing neuroimaging findings at the time of PET.

[†] Derived from the Short Test of Mental Status.

[∞] out of 9 possible exclusions included, as shown in the table: CNS-related exclusions, neuroimaging findings at the time of PET scan, serious risk of suicide (past 1 year), psychiatric hospitalization (past 6 months), malignant neoplasms (past 5 years), alcohol or substance abuse (past 2 years), liver impairment (past 6 months), end-stage renal disease (past 6 months), autoimmune disorder (past 1 year).

[‡] Diabetes, hypertension, dyslipidemia, congestive heart failure, coronary artery disease, based on medical record review by expert nurse abstractors; obesity (BMI≥30) as measured at baseline; 3 missing.

[§] Based on the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 / ICD-10) codes from the participants' electronic health records (EHR) using the REP medical records linkage system resources, unless otherwise specified. Detailed eligibility criteria used are provided in the Supplemental Materials Appendix. The Mayo Clinic Study of Aging neuroimaging studies assessed neuroimaging findings.

[||] Considered brain cancer, Parkinson's disease, epilepsy, coma/brain damage, or intracranial injury.

[£] Did not consider codes for benign tumors, basal cell carcinoma, squamous cell carcinoma, other non-melanoma skin cancers, or localized prostate cancer, or cancer of the lip.

[#] Considered Lupus, Sjogren's syndrome and rheumatoid arthritis or other inflammatory arthropathy.

been different (e.g., past 3 years for history of cancer in the Pittock et al. study and past 5 years in the present study). One exclusion criterion that was satisfied by Pittock et al. but was not possible to operationalize in the current study was the review of the electronic medical record of participants that covered the lecanemab inclusion criteria for cardiopulmonary conditions the past 1 year that were not "stably and adequately controlled." Such medical record review was not available in the current study, and other differences in criteria used were the neuroimaging measures included. The Appendix in the Supplemental materials provides all the details of the eligibility criteria used in the current study.

Neuroimaging findings, central nervous system exclusions, and history of malignancy were the major exclusions in the present study. Strict eligibility criteria in clinical trials (e.g., for population homogeneity, reduction of safety and tolerability concerns) might result in highly selected participants with underrepresentation of those with common conditions in older adults, reducing the generalizability of the findings in the community [33]. As anti-beta amyloid mAbs and other disease-modifying therapies (DMT) are becoming available for a growing aging population, such treatments need to be discussed in older populations where abnormal neuroimaging findings, comorbidities, and history of malignancy are more common with aging. Strong interdisciplinary collaborations, including experts in the aging field, will be needed in all DMT development stages (from research development to clinical application) to assess the effectiveness of treatments in the community and assure safe and accessible AD treatments with appropriate follow-up care [34].

Clinical trials inform prescribing guidelines, and there might be a gap in treatment decision information for patients outside of the strict clinical trial eligibility criteria. Appropriate use recommendations (AUR) have been published for aducanumab [35] and lecanemab [36] use and recently presented at the Clinical Trials on Alzheimer's Disease (CTAD) 2024 meeting for donanemab use [37]. The AUR try to bridge the gap between clinical trials and real-world clinical practice and offer insight into using new therapies [37].

In addition, although the Alzheimer's disease and related dementias (ADRD) burden is higher in African American/Black and Hispanic/Latino populations, these and additional racial and ethnic groups are still underrepresented in ADRD randomized clinical trials, limiting our understanding of the impact of novel treatments on diverse populations [38]. Thus, the Alzheimer's Clinical Trials Consortium (ACTC) – a national consortium funded by NIH - seeks to develop and implement novel strategies for efficient recruitment, randomization, enhanced diversity, and retention in ADRD clinical trials [38].

Because of the resource-intensive nature of anti-amyloid treatment, estimates of the eligible population are important for clinical planning and policymaking. Parallel efforts in developing appropriate resources for the patients and families, improving health care planning and infrastructure to minimize waitlists for specialists, MRI and PET scans, infusion centers, and development of inexpensive and accessible screening for AD biomarkers (e.g., using plasma biomarkers) need to be considered. In addition, rigorous post-marketing surveillance and the use of patient registries could help gather information necessary for potential mAbs therapy adjustments [36], as patient registries can provide important information on treatment effectiveness and safety. Safety risks, such as amyloid-related imaging abnormalities (ARIA) or infusion-related reactions can occur after anti-beta amyloid mAbs treatments, like donanemab. Although ARIA is usually asymptomatic, it can be life-threatening and rarely fatal, and APOE $\varepsilon 4$ homozygotes are at higher risk for incident ARIA [36,39]. Registries like the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) collect clinical, imaging, and safety data over time from patients treated with the new AD therapies and provide real-world data from diverse clinical settings [40]; ALZ-NET will gather evidence of treatment effectiveness and side effects, share useful information for needed treatment adjustments, and educate clinicians, researchers, and patients [36,40–42].

To qualify for treatment for any of these anti-amyloid treatments, patients must have early symptomatic AD and a positive amyloid biomarker. In addition, the donanemab trial used the brain tau burden as a central biomarker, and trial participants needed to be *T*+, which was assessed by visual inspection in the current study. Based on the phase 3 donanemab trial findings [10], participants with high baseline tau burden appear to benefit less than those with low/medium tau burden, possibly supporting the hypothesis that too high tau burden might imply the disease is past the stage of responsiveness to amyloid reduction [8]. The present study did not differentiate between high and low/medium tau accumulation in the brain since the definition for determination of tau PET burden was not available for replication. The study also assessed the characteristics and exclusion criteria of the participants in the sample who had early symptomatic AD (had also fulfilled the inclusion criteria of being 60–85 years old, with an MMSE score of 20–28) without considering the tau PET assessment, which resulted in a higher number of participants eligible with this approach. Of note is that the FDA approval of donanemab use [10] does not consider or require a tau PET.

In our study, we did not exclude participants who did not report a study partner (5 of the *T*+ participants in Table 1); we considered this eligibility criterion satisfied, as the motivation for a study partner might be different in an observational study than in a clinical trial where the partner is involved in decision making and support systems for treatment adherence and safety monitoring [37]. In addition, anticoagulant use was not considered an exclusion criterion by the present study, while the AUR for donanemab presented at CTAD2024 recommends excluding patients on anticoagulation until more data are collected by clinical trials and real-world use [37]. The AUR for donanemab is expected to be published in the near future.

MCSA participants follow the same evaluation protocol approximately every 15 months when invited for the follow-up visits. These visits are not triggered by symptoms, and evaluators are blind to any previous cognitive diagnosis. Thus, it is possible that the disease was detected at an earlier stage for some of the participants in the study than when their symptoms would trigger a clinical visit with their care team. This is a strength of the study, and similarly, additional efforts are needed for early disease detection and the availability of accurate biomarkers of disease pathology in clinical practice so as to have the opportunity for early intervention [43]. However, it is reasonable to expect that, in general, patients visiting memory clinics would be further along in the clinical symptomatology, and thus, our eligibility estimation could be optimistic, including healthier volunteers earlier in the disease process; this is also supported by the observation that 31 % (11 of 35) of the participants with dementia were excluded based on the MMSE criterion, while only 3 % (24 of 782) participants with MCI were excluded based on the same criterion. There is still much work to be done on early detection and, at the same time, on the development of easier-to-administer DMTs [44].

The main focus in clinical practice is estimating the number of patients likely to seek an evaluation for amyloid-lowering treatment and the number likely to meet treatment criteria. In MCSA, neuroimaging is not required but offered to all participants as an option; thus, we cannot directly estimate the number of likely eligible for treatment, beginning at the start of the funnel in Fig. 1, unless we make specific assumptions outside the information provided by the present study. For example, the prevalence of amyloid positivity in persons with MCI has been estimated previously [45] and ranges from 0 (50–60 years old) to 16.4 % (80–89 years old) in Olmsted County (i.e., MCSA sampling frame). Thus, using this information and the percentage of eligible participants with *A*+ MCI/mild dementia (as suggested in Table S1), we could extrapolate that a much smaller overall percentage of participants with MCI/mild dementia would be eligible for the donanemab trial at the beginning of the funnel in Fig. 1. However, this would be a very crude estimation as there are many contingencies besides amyloid positivity, some of which we addressed; this eligibility percentage is made smaller by how carefully eligible persons are vetted, and further studies could provide more detail.

The study has several strengths. The MCSA provides comprehensive cognitive evaluations and state-of-the-art neuroimaging that provides reliable measures of AD imaging biomarkers. In addition, the REP medical records linkage system allows us to retrieve the history of comorbidities. However, the study is not without limitations. Comorbidities' misclassification is possible with the use of ICD-9 or ICD-10 codes. We could not define all eligibility criteria given the available data. Tau PET was implemented in 2015; thus, fewer MCSA participants had tau PET data available. We acknowledge that we cannot account for other unmeasured factors (socioeconomic factors, distance from treatment centers, etc.) that would not allow patients to participate safely in the monitoring, accessibility, and resource-intense requirements of safe therapy. There is a higher median household income in Olmsted County (vs. the US population) [12], and the study sample had high mean years of education. The study sample was not racially and ethnically diverse, again reflecting the characteristics of Olmsted County. Evaluation of the eligibility criteria in diverse populations is essential.

Study findings suggest that a small percentage of individuals with biomarker-confirmed early symptomatic AD would qualify for the donanemab phase 3 clinical trial. Main exclusions were abnormal neuroimaging findings, CNS exclusions, and history of malignancy, which are also common conditions in older adults. Additional efforts are needed with strong interdisciplinary collaborations, including experts in the aging field, so that the fraction of participants with early symp-

tomatic AD eligible for anti-amyloid trials and treatments substantially improves.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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CRediT authorship contribution statement

Katherine E. Jones: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Jeremiah A. Aakre:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Anna M. Castillo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Vijay K. Ramanan:** Writing – review & editing, Investigation. **Walter K. Kremers:** Writing – review & editing, Supervision, Methodology, Investigation. **Clifford R. Jack Jr:** Writing – review & editing, Investigation, Funding acquisition. **Prashanthi Vemuri:** Writing – review & editing, Investigation, Funding acquisition. **Christopher G Schwarz:** Writing – review & editing, Methodology. **Val J. Lowe:** Writing – review & editing, Methodology, Investigation. **David S. Knopman:** Writing – review & editing, Investigation, Funding acquisition. **Ronald C. Petersen:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Jonathan Graff-Radford:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Maria Vassilaki:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors have not used any AI to generate text. They have used Grammarly to detect and correct spelling and grammatical errors.

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Data Access Statement

The Mayo Clinic Study of Aging makes data available to qualified researchers upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100088.

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