The Journal of Prevention of Alzheimer's Disease 13 (2026) 100625

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Editorial

Eligibility of men vs. women in Alzheimer's trials: Inclusive vs. representative

ARTICLE INFO

Keywords:
Trials
Inclusion
Representation

High quality research should be prospectively designed and must recruit a sample that facilitates testing the scientific hypothesis under study. The highest level of scientific evidence that can be achieved comes from randomized, controlled trials. The stakes for these studies are also highest, as the evidence they produce will guide clinical practice. Enrolling a sample that is overly homogenous in clinical trials may prevent learnings related to effect modification among key subgroups [1]. For late phase trials especially, the representativeness of the sample enrolled could also affect clinical interactions centered around the intervention's consistency of benefits and the willingness of patients to follow a prescriber's recommendations [2]. Thus, if certain groups are systematically excluded from trials, for example due to differential eligibility based on specific enrollment criteria, the ramifications to clinical practice can be significant.

In this issue of *Journal of Prevention of Alzheimer's Disease*, Exalto and colleagues leveraged 25 years of data from the clinical program at Vrije Universiteit in Amsterdam to address the research question of whether women and men are equally likely to be eligible for clinical trials in symptomatic Alzheimer's disease (AD) [3].

The authors extracted eligibility criteria from 608 AD drug trials posted to clinicaltrials.gov, harmonized these criteria using machine learning, and identified the five most frequently used criteria across trials. These five criteria were relatively consistently implemented, present in 59–84% of the trials used as data sources, and included: 1) no other central nervous system disorder likely to contribute to cognitive impairment, 2) participation of a caregiver, or study partner, 3) scoring within a specific range on the mini-mental state exam (MMSE), 4) the absence of vascular and mental health comorbidities, and 5) no contraindications for study procedures, particularly those required to assess AD biomarkers.

Applying these most common eligibility criteria to more than 25 years of clinical records at their single high-volume tertiary care center of excellence, the authors found that 33% of male and 23% female patients would qualify for trials. The overall estimates of eligibility are somewhat higher than previous similar exercises [4] and recent assessments of clinical appropriateness for anti-amyloid treatments that were derived from phase 3 trial enrollment criteria [5]. These differences are likely due to the methodological emphasis on a limited number of enrollment criteria, which are generally much more extensive in actual trials, include specific requirements related to the treatment under study and its mechanism of action, and now frequently include biomarker positivity to confirm AD as a cause of cognitive impairment.

The difference in overall eligibility rates between women and men was statistically significant. The greatest difference in eligibility between the groups based on sex was due to the availability of a study partner (77% of men were eligible compared to 64% of women). This, as pointed out by the authors, illustrates a key bias in AD trials—overrepresentation of spousal dyads. Men with AD are more likely to have a spouse, whereas women with AD have often outlived their partners. The authors expand on the potential contributors to the observed sex difference, suggesting that differences between the sexes (of family members) also could contribute diagnosis-seeking behaviors; a key first step for most patients in trial participation. Most patients seen at the authors' clinical center were men. The explanation that sex differences in diagnosis-seeking contributed to the overall difference in eligibility may be corroborated by the observed second-greatest differential between the sexes in eligibility—the MMSE. Most female patients in their clinic, and sizably more female than male patients (54%vs. 32%), were ineligible for enrollment based on MMSE scores (20 or greater) at their first diagnostic visit, suggesting more severe cognitive impairment at presentation among female patients. The authors hypothesize that available family members, particularly spouses, are key to seeking care. The availability of spouses and potential differences between the sexes in the urgency of seeking care, they offer, are likely to contribute to the observed differences in trial eligibility.

The results are important. They should spark key questions about social barriers to early diagnosis, as well as timely referral to trial centers for participation in clinical trials. Limitations should also be noted, particularly the issue of generalizability for results from this single, Northern European tertiary care center to the increasingly global conduct of AD trials.

Finally, the authors make the case that differential exclusion may

https://doi.org/10.1016/j.tjpad.2026.100625
Received 8 June 2026; Accepted 8 June 2026
Available online 13 June 2026

contribute to women being underrepresented in AD trials—that is, that the proportion of trial participants who are women is generally lower than the estimated 64% of dementia sufferers who are women. This also should warrant further consideration. Trials are typically powered to demonstrate differences between intervention and placebo. While identifying signals of effect modification when they are present is critical, trials are generally not powered to detect such effects in the absence of earlier observations and strong mechanistic rationale for treatment effect heterogeneity with respect to safety and/or efficacy. Underrepresentation of non-spousal dyads, most of whom would include female patients (and female study partners) offers the practical opportunity to increase recruitment – a consistent challenge to AD drug development. But trials are not charged with estimating prevalence or incidence at the population level. They instead have explicit and focused hypothesis-testing goals that are restricted to inference for contrasts between randomized arms. And so, aside from this practical issue and the possibility of strong effect modification by sex, is enrolling a majority female participants, but less than the population estimated proportion of disease sufferers, truly scientifically inadequate?

No artificial intelligence was used in drafting this manuscript.

Author disclosures

JDG: research grants from NIA, Alzheimer's Association, BrightFocus Foundation, Lilly, Biogen, Genentech, Eisai. Personal compensation for consulting to Valuate Health and Genentech; editorial service to Alzheimer's & Dementia. Travel paid for by the Alzheimer's Association.

DLG: Consultant to: Pfizer, Roche/Genentech, Seattle Genetics, Merck, Novo Nordisk, Novartis, Intellia, Atossa, Astrazeneca, Acerta, Biomarin, Oncoverity, Amicus, Eli Lilly, Neurocrine, Generate, Apollo, E-Star, Janssen, Arrivent, UniQure, 3D Communications, Travere, AbbVie, Aquestive, GlaxoSmithKline, Apollo, Kinaset, Moderna, Insmed, LB Pharma, UniQure.

JDG and DLG are supported by P30 AG066519.

CRediT authorship contribution statement

Joshua D. Grill: Conceptualization, Writing – original draft, Writing – review & editing. **Daniel L. Gillen:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joshua Grill reports a relationship with Genentech that includes: consulting or advisory. Joshua Grill reports a relationship with Valuate Health that includes: consulting or advisory. research grants from NIA, Alzheimer's Association, BrightFocus Foundation, Lilly, Biogen, Genentech, Eisai. Personal compensation for consulting to Valuate Health and Genentech; editorial service to Alzheimer's & Dementia. Travel paid for by the Alzheimer's Association. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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