A call to action to address sex differences in Alzheimer's clinical trials

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Historically, scientific findings from male *in vitro* and *in vivo* models have formed the gold standard of medical knowledge. This approach, exacerbated by low female representation in medical research and a dearth of studies investigating sex differences, has led to significant public health, clinical and humanitarian implications, as well as economic consequences. A cardinal example from the field of cardiology was the discovery of critical sex-specific treatment effects were only discovered through ad hoc observational analyses, years after the results of clinical trials had been published. There is a pressing need to study and report sex differences across the field of medicine, but most crucially now in Alzheimer's disease (AD).

With decades of AD drug research failing to show efficacy, and even induced excess toxicity, the headline findings from the CLARITY-AD clinical trial with lecanemab offered some light at the end of the tunnel.[1] Lecanemab's ability to clear large soluble protofibrils of beta-amyloid (Aβ) in the brain and moderately slow the progression of cognitive decline[1] was hailed as "momentous" by Alzheimer's Research UK. The U.S. Food and Drug Administration subsequently authorized its use via the accelerated approval pathway. This came after the controversial approval of aducanumab, based on a retrospective re-analysis result from the EMERGE and ENGAGE trials.[2] Not only does uncertainty exist around the clinical efficacy of both drugs, substantial financial costs associated with treatment could pose an immense burden on patients, families, and healthcare systems.

All three recent clinical trials with anti-amyloid agents (CLARITY-AD, EMERGE, ENGAGE) had a balanced representation of female enrolment (52.3%, 51.5%, 52.4%, respectively). Disappointingly, sex-disaggregated analyses were not expanded in the main reporting of the trial results, particularly when examining sex by treatment interactions, despite indications of meaningful differences. Upon closer inspection of the CLARITY-AD reporting, subgroup analyses buried in the supplementary material revealed noteworthy sex differences. Specifically, the cognitive benefits of the drug (in primary endpoint tests of the Clinical Dementia Rating scale Sum of Boxes (CDR-SB) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-COG)) were evident primarily in men.[1] This was similarly observed in the EMERGE trial, where reduced cognitive decline (again in CDR-SB and ADAS-COG) was evident in men but not in women.[2] These preliminary findings support mounting evidence that drug efficacy, including pharmacokinetics and pharmacodynamics, can be influenced by biological sex. However, currently there is a dearth of published clinical and biomarker data on sex differences in AD trials, since sex stratification and evidence of interactions are not considered.

Several potential rationales exist for the possible sex differences in these trials. One well-documented finding is that women exhibit higher tau burden relative to men,[3, 4] and the synergistic effect of sex with *APOE* genotype has consistently revealed that female *APOE* ε4 carriers exhibit higher tau burden and risk for progression to dementia.[5] Moreover, transcriptomes linked to the X chromosome have also been implicated in AD pathogenesis in a sex-specific manner.[6] While the picture surrounding sex differences in incidence rates for AD remains somewhat convoluted, with a dependence on other intersectional factors such as

age, race, ethnicity, socioeconomic status, geographical regions, and gender-related comorbidities, it is increasingly clear that women have a greater lifetime risk of dementia due to greater longevity, and a disproportionate contribution from female-specific reproductive factors to elevated dementia risk and neuropathology.[3] The impact of pathology on clinical outcomes also differs by sex, with women expressing cognitive resilience in the face of pathological load in preclinical AD,[7] but these compensatory mechanisms are lost with increasing cognitive impairment.[8] It is possible that any one or all of these factors are playing a role in therapeutic sex differences. Understanding potential drivers of the differences in therapeutic effects will require further exploration of the clinical trial data, as well as targeted efforts to examine sex-specific treatment effects in future trials.

If the potential benefits of this new generation of AD drugs are specific to men, this is likely to further widen the gap which already exists in a multitude of health conditions between women and men. Without a careful interpretation of the sex differences in AD treatment effects, and subsequently accounting for these differences in clinical practice, inequities in healthcare can occur. For instance, women with early signs of cognitive decline might continue to accumulate adverse neuropathological burden and experience decline in cognition and function, but with the perception of being prescribed with the most appropriate guideline-based care. This situation echoes that from cardiovascular medicine, which until only recently did not have optimised cardiovascular therapeutics strategies for women.[9]

The recent reporting of AD trials still perpetuates the recurring pattern of research studies failing to report outcomes disaggregated by sex (or gender), in such a way as to judge the effect of sex on treatment outcomes. Our paper found that only eight of 118 identified dementia trials reported sex-disaggregated outcomes.[10] This is despite women representing approximately 60% of all AD dementia patients, and publication guideline such as the Sex and Gender Equity in Research (SAGER) policy, and government funding bodies (e.g., National Institutes of Health) requiring sex-balanced study designs and sex-disaggregated analyses. As such, these data collection and reporting standards should be continuously recommended, or even mandated.

It is crucial to note that the lack of sex-disaggregated data reporting in clinical trials is not unique to AD research but is a pervasive issue across many areas of medicine. Given the unique complexities of AD pathophysiology and the disproportionate impact of AD on women, it is especially important for AD research to adopt rigorous standards for sex-disaggregated analyses, starting with increasing the representation of women to better reflect clinical populations.[10] Therefore, we call for comprehensive investigations into sex differences associated with treatments in existing and integration into future AD (and related dementia) clinical trials. This includes taking baseline AD biomarker and genetic burden by sex into consideration, the inclusion of sex disaggregated results as a routine standard, and even the initiation of powered trials that can include sex disaggregated results as a primary endpoint. Routine examination and reporting of reproductive characteristics of women and men in clinical trials should be considered to augment the biomarker information. Reporting of sex differences in drug tolerability and adverse events, and exploring potential sex-specific mechanisms of therapeutic response are warranted. Pre-specification of these analyses prior to

trial commencement can help establish robust evidence for sex differences, leading to sex-specific recommendations for dosing and drug applicability.

As we anticipate more AD drugs to be approved and entering the market, it is imperative to ensure that sex differences in treatment effects are well understood before they are prescribed to patients. Without considering sex (and gender) differences, dementia researchers are poorly serving clinicians and their patients.

References

1. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, et al. Lecanemab in Early Alzheimer's Disease. *New England Journal of Medicine*. 2022;
2. Budd Haeberlein S, Aisen P, Barkhof F, Chalkias S, Chen T, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *The Journal of Prevention of Alzheimer's Disease*. 2022;9(2):197-210.
3. Buckley RF, O'Donnell A, McGrath ER, Jacobs HI, Lois C, et al. Menopause status moderates sex differences in tau burden: a Framingham PET Study. *Annals of Neurology*. 2022;
4. Buckley RF, Mormino EC, Rabin JS, Hohman TJ, Landau S, et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA neurology*. 2019;76(5):542-551.
5. Hohman TJ, Dumitrescu L, Barnes LL, Thambisetty M, Beecham G, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA neurology*. 2018;75(8):989-998.
6. Davis E, Solsberg C, White C, Miñones-Moyano E, Sirota M, et al. Sex-Specific Association of the X Chromosome With Cognitive Change and Tau Pathology in Aging and Alzheimer Disease. *JAMA Neurology*. 2021;78(10):1249-1254.
7. Ossenkoppele R, Lyoo CH, Jester-Broms J, Sudre CH, Cho H, et al. Assessment of demographic, genetic, and imaging variables associated with brain resilience and cognitive resilience to pathological tau in patients with Alzheimer disease. *JAMA neurology*. 2020;77(5):632-642.
8. Buckley RF, Scott MR, Jacobs HI, Schultz AP, Properzi MJ, et al. Sex mediates relationships between regional tau pathology and cognitive decline. *Annals of neurology*. 2020;88(5):921-932.
9. Bairey Merz CN, Andersen H, Sprague E, Burns A, Keida M, et al. Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women: The Women's Heart Alliance. *J Am Coll Cardiol*. Jul 11 2017;70(2):123-132.
10. Pinho-Gomes AC, Gong J, Harris K, Woodward M, Carcel C. Dementia clinical trials over the past decade: are women fairly represented? *BMJ Neurol Open*. 2022;4(2):e000261.