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Letter to Editor
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Sex Differences in Treatment Effects of Lecanemab and Donanemab: A Bayesian Reanalysis of CLARITY AD and TRAILBLAZER-ALZ 2

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Letter to Editor

We read the article by Teipel, et al. with concern. It claims evidence of sex specific differences in the efficacy of lecanemab based on a Bayesian reanalysis of subgroup data from two phase 3 trials. Although framed as a methodological refinement, the analysis reflects a biased and fatally flawed interpretation of subgroup results. Readers will be misled regarding the strength and credibility of the underlying evidence.

Neither Clarity AD nor Trailblazer ALZ2 was designed or powered to assess treatment by sex interactions. Subgroup analyses by sex were exploratory, and subject to the vagaries of post-hockery and multiplicity. The primary analyses in both trials demonstrated statistically persuasive efficacy in the overall populations. In this context, any inference of differential efficacy by sex must meet a high evidentiary bar, including strong biological plausibility and independent replication. These criteria were not satisfied in the lecanemab and donanemab trials.

A core weakness of the article is the implication that the Bayesian approach avoids the well-known and well-accepted fallacies of subgroup analysis. Nothing could be further from the truth. Bayesian analyses must consider all available prior evidence. Suppose a researcher carries out retrospective subgroup analyses of data from a positive clinical trial until finding a subgroup for which the result is negative. In view of the inherent variability in the disease and the end point, he is very likely to find at least one negative subgroup, whether or not there is a true negative. So, the Bayes factor is essentially 1.0 and the researcher's observation is noninformative.

The absence of biological plausibility further undermines the authors' conclusions. There is no established mechanism by which amyloid targeting antibodies would be expected to demonstrate materially different clinical efficacy between women and men. The speculative post hoc explanations offered ranging from tau burden to hormonal effects have no apriori biological support or rationale.

Of particular concern are the clinical and regulatory implications drawn by the authors. Statements suggesting that lecanemab is "six times more likely to be ineffective than effective in women," or that future trials should be powered specifically for sex-based interaction effects, have no support whatever. Publishing such statements is not only inappropriate, it is unethical. Promoting post hoc subgroup findings in this manner risks misinforming clinicians and patients and may lead to inappropriate treatment decisions. History offers many cautionary examples in which post hoc sex specific findings prompted confirmatory trials that ultimately proved negative.

In summary, the analysis by Teipel, et al. exemplifies the subgroup fallacy articulated extensively in statistical and clinical literature, including from me [1-9]. Recasting underpowered, post hoc subgroup contrasts in Bayesian terms does not confer evidentiary validity. The appropriate interpretation of the available data is that lecanemab and donanemab demonstrate efficacy in their overall trial populations, with positive treatment effect in the randomized population, including females as well as males. Any suggestion to the contrary has no empirical or scientific basis.

I respectfully request that the journal retract the Taipel et al. article.

References

1. Berry DA. Multiple Comparisons, Multiple Tests, and Data Dredging: A Bayesian Perspective (with discussion). In Bayesian Statistics. 1988;3:79-94.
2. Berry DA. Subgroup analyses. Biometrics. 1990;46(4):1227-30.

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3. Berry DA, Thor A. Scientific Inference and Predictions; Multiplicities and Convincing Stories: A Case Study in Breast Cancer Therapy (with discussion). In Bayesian Statistics. 1995;5:45-67.

4. Gopalan R, Berry DA. Bayesian multiple comparisons using Dirichlet process priors. J Am Statistical Association. 1998;93(443):1130-9.

5. Berry DA, Hochberg Y. Bayesian perspectives on multiple comparisons. J Statistical Planning Infer. 1999;82(1-2):215-27.

6. Berry SM, Berry DA. Accounting for multiplicities in assessing drug safety: A three-level hierarchical mixed model. Biometrics. 2004;60(2):418-26.

7. Berry DA. The difficult and ubiquitous problems of multiplicities. Pharm Stat. 2007;6(3):155-60.

8. Berry DA. Multiplicities in cancer research: Ubiquitous and necessary evils. J Natl Cancer Inst. 2012;104(15):1124-32.

9. Berry DA. P-values are not what they're cracked up to be. Online Discussion: ASA Statement on Statistical Significance and P-values. The American Statistician. 2016.