The Journal of Prevention of Alzheimer's Disease 12 (2025) 100119

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

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

Letter to the Editor

Reply to: Enhancing Statin Research for Alzheimer's Prevention: Suggestions for Future Studies and Policy Implications

We greatly appreciate Dr. Zhong and colleagues for their thoughtful commentary on our recently published article "Association of statins use and genetic susceptibility with incidence of Alzheimer disease" [1]. And their constructive suggestions for public health policy were of great value.

1. Reverse Causality and Mendelian Randomization

The commentators rightly highlighted the potential for reverse causality in observational studies, where AD-related comorbidities (e.g., cardiovascular disease) might influence statin use rather than statins directly causing AD. Actually, reverse causality is a potential bias which is inevitable on observational studies. At this point, we have taken some measures to minimize this bias. On the one hand, participants with dementia at baseline had been excluded from analyses in this study. On the other hand, Cox proportional hazards models were used to estimate the effects of statins based on longitudinal data, ensuring that the outcomes occurred after the exposure. Therefore, we believe that the bias from reverse causality has been reduced greatly in this study. Nevertheless, we also agree that Mendelian randomization (MR) is a promising approach to establish causality. However, since statins use is affected by clinical decisions rather than genetics, MR might be less suitable for examining association of statins use with AD directly. Instead, MR could be effectively applied to estimate the relationship between AD and phenotypes associated with the mechanism of statins action, such as LDL cholesterol levels [2].

2. Cognitive Assessments and Domain-Specific Effects

As noted in the commentary, our study mainly focused on the relationship between statins and global cognitive scores instead of specific cognitive domains, and also lacked longitudinal assessments to clarify their correlation. In fact, this study was aimed to investigate the effect of statins on AD and the moderating role of genetic factors. For this part, we constructed longitudinal assessments to reveal association of above. As the commentary pointed out, specific domains of cognitive impairment such as episodic memory and executive function are more sensitive to AD. As far, the impact of statins use on specific cognitive domains like episodic memory or executive function has been extensively explored [3–6], whose findings were vital foundations for this study.

3. Competing Risks and Fine-Gray Models

We agree that some comorbidities such as stroke, diabetes, or cardiovascular diseases may confound the results. Therefore, these confouders have been adjusted for in all models. Moreover, we also conducted a series of interaction analyses based on these medical histories and obtained significant results (referring to the section "Joint effects and interactions of statins use with other individual-related factors", as well as Supplemental Table 8 and (c), (d), (e) in Supplemental Figure 2). Meanwhile, we believe that death is a more important competing event rather than stroke, diabetes, or cardiovascular diseases. Thus, we established a competing risk model in which death as a competing event in the sensitivity analysis, and the results were still stable and reliable.

We thank Dr. Zhong and colleagues for their insightful suggestions regarding the implications of our study on AD and the proposed public health strategies. Their emphasis on the importance of personalized treatment strategies and the integration of genetic screening in the context of AD prevention aligns well with the core of our research. In this study, these findings demonstrate the moderating role of genetic factors in the effect of statins on AD, might potentially serve as a scientific basis for the integration of genetic screening into routine healthcare practices as they suggested.

Conflict of Interest

The authors do not have conflict of interest.

References

[1] Ye Z, Deng J, Wu X, Cai J, Li S, Chen X, Xin J. Association of statins use and genetic susceptibility with incidence of Alzheimer's disease. J Prev Alzheimers Dis 2025;12:100025.
[2] Li Y, Liu H, Shen C, Li J, Liu F, Huang K, et al. Association of genetic variants related to combined lipid-lowering and antihypertensive therapies with risk of cardiovascular disease: 2×2 factorial Mendelian randomization analyses. BMC Medicine 2024;22.
[3] Royall DR, Palmer RF. Statin use moderates APOE's and CRP's associations with dementia and is associated with lesser dementia severity in ϵ4 carriers. Alzheimer's & Dementia 2023.
[4] Geifman N, Brinton RD, Kennedy RE, Schneider LS, Butte AJ. Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer's disease. Alzheimer's Research &amp. Therapy 2017;9.
[5] Dagliati A, Peek N, Brinton RD, Geifman N. Sex and APOE genotype differences related to statin use in the aging population. Alzheimers Dement (N Y) 2021;7:e12156.
[6] Gentreau M, Rukh G, Miguet M, Clemensson LE, Alsehli AM, Titova OE, et al. The Effects of Statins on Cognitive Performance Are Mediated by Low-Density Lipoprotein, C-Reactive Protein, and Blood Glucose Concentrations. The Journals of Gerontology: Series A 2023;78:1964–72.

DOI of original article: 10.1016/j.tjpad.2025.100118

https://doi.org/10.1016/j.tjpad.2025.100119

Available online 15 March 2025

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