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LETTER

Comment on "The Effect of Epigenetic Age Acceleration on Atopic Dermatitis: A Mendelian Randomization Study" [Letter]

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Dear editor

I have read with great interest the manuscript by Xin et al, which explores the causal relationship between epigenetic age acceleration and AD using MR.[1] The study addresses an important and emerging topic in dermatology and aging research. However, several methodological and interpretive considerations not addressed in their manuscript merit further examination to enhance the robustness of their conclusions.

First, a notable discrepancy exists in the reported sample size for the AD GWAS from FinnGen. The manuscript indicates 394,476 cases and 421,381 controls, which suggests a possible misinterpretation of the FinnGen dataset, as this would imply an unusually high case prevalence (~48%) inconsistent with established AD epidemiology.[2] According to the official FinnGen Release 11 documentation, the correct numbers for the endpoint "L12_ATOPIC" are 38,683 cases and 474,647 controls.[3] This difference in case numbers may stem from conflating the total number of individuals with phenotype data in FinnGen (~394,000) with AD-specific cases or from a broader classification of skin conditions. Clarification of the correct case and control counts would be valuable for assessing the reliability of the downstream analyses. The authors are encouraged to verify the source of this data and, if necessary, re-analyze using the publicly available summary statistics to ensure accuracy.

Building on this foundational data concern, potential sample overlap between the FinnGen cohort and the epigenetic age GWAS participants—both primarily from European populations—should also be considered, as even modest overlap can introduce bias in MR estimates by violating core assumptions and shifting results toward observational associations.[4,5] This factor may contribute to the borderline significance ($p = 0.046$) observed for HannumAge acceleration, highlighting the need for explicit checks or adjustments in future studies to maintain the validity of causal inferences.

Furthermore, while the authors appropriately acknowledge that HannumAge reflects changes in immune cell composition,[6] this specificity raises the possibility of mediated pleiotropy as an alternative explanation for the findings. Given that many AD-associated genetic variants influence circulating leukocyte populations independently of disease processes,[7] the association could arise from genetic effects on immune cell abundance that affect both AD risk and HannumAge acceleration through separate pathways, potentially challenging the exclusion restriction assumption in MR.[4,5]

In addition, the clinical heterogeneity inherent in registry-defined AD within FinnGen, which encompasses a spectrum from pediatric-onset to adult-persistent cases and varying severity levels,[8,9] warrants attention. Epigenetic age acceleration may interact differently with these subtypes, such as associating more strongly with chronic adult AD compared to transient childhood forms. Without stratification by age of onset or disease trajectory, the reported effect might represent an averaged signal across diverse phenotypes, potentially diluting or confounding the true relationship.

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In conclusion, these considerations underscore the importance of rigorous data verification, assumption testing, and phenotype refinement in MR studies of epigenetic aging and AD. Addressing them could refine our understanding of biological aging mechanisms in dermatological conditions, improve methodological standards in the field, and inform targeted.

Data Sharing Statement

No new data has been generated, all references are cited in the letter.

Author Contributions

The author made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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